

Exhibit 1

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM
POWDER PRODUCTS MARKETING, SALES
PRACTICES AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (MAS) (RLS)

THIS DOCUMENT RELATES TO ALL CASES

EXPERT REPORT OF ANALISA DIFEO, Ph.D.

Date: May 28, 2024



Analisa DiFeo, Ph.D.

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I. BACKGROUND AND QUALIFICATIONS

I am a Professor (with tenure) in the Department of Pathology and Obstetrics & Gynecology at the University of Michigan Medical School. I have more than 20 years of experience in biomedical research focused on ovarian cancer. I have a broad background in ovarian cancer genetics and biology, with specific training and expertise in cancer biology, chemotherapy resistance, tumor initiation, and development of patient-based models. The focus of my laboratory spans the continuum of translational research, beginning with an in-depth analysis of patient tumors and progressing to a functional assessment of key genetic drivers of ovarian cancer progression and the development of a novel therapeutic approach to abrogate these drivers to uncover therapies that will improve ovarian cancer patient survival. In my role as a translational research scientist, I oversee a translational ovarian cancer research laboratory, which I independently started in 2012. In addition, I have organized and founded several large translational research programs at a variety of different institutions that focused on developing a team of diverse investigators interested in gynecological cancers and developing well-characterized patient-relevant gynecological cancer tumor models that have been used by numerous individuals in the scientific community and industry partners, leading to the discovery of novel therapeutic targets, biomarkers, and drugs. Currently, I am also the Director of the Michigan Ovarian Cancer Science and Innovation Consortium (MOSAIC) and the co-Principal Investigator of the gynecologic cancer tumor repository. Samples collected from this tumor bank have been shared with more than 30 labs across the world, have resulted in more than 30 peer-reviewed publications, and led to more than \$16 million in funding from philanthropic gifts, federal grants, and industry-sponsored research agreements.

Since the inception of my laboratory, it has been funded continuously through numerous federal, foundation and industry grants, primarily focused on ovarian cancer, including, but not limited to, numerous Department of Defense awards, several Mary Kay Foundation awards, Ovarian Cancer Research Alliance, Eli Lilly Research Award, and R21 and R01 funding through the National Cancer Institute. We have published more than 70 original research articles (>4800 citations; h-index 39) and have been granted a patent on Biomarker Associated with Risk of Melanoma Recurrence, US Patent **US20150218649A1**, and filed another patent for Compositions and Methods for Treating Cancer, Worldwide Patent **WO2017176756A**.

I received my Bachelor of Science in Biochemistry at SUNY Binghamton in 2001, and my Ph.D. in Cancer Genetics from Mount Sinai School of Medicine (now named Icahn School of Medicine) in New York in 2008, where I played a central role in defining alternative splicing of the KLF6 gene family as a key regulator in ovarian cancer. We found that both KLF6 and its oncogenic splice variant, KLF6-SV1, are key regulators of epithelial ovarian cancer pathogenesis. Our findings were the first to demonstrate that a majority of ovarian cancer tumors have increased expression of the oncogenic KLF6-SV1 isoform, and that this variant is a novel anti-apoptotic protein that regulates chemotherapy response. Through this work, I received the AstraZeneca Scholar-in-Training Award from the American Association of Cancer Research, and the Terry Krulwich Doctoral Dissertation Award from Mount Sinai School of Medicine. In 2012, I was appointed an Assistant Professor in the Division of General Medical Sciences (Oncology) at Case Western Reserve University School of Medicine and started my own research laboratory. Soon after, I was honored with The Norma C. and Albert I. Geller Designated Professor in Ovarian Cancer Research in 2014 for my efforts in developing the first Gynecologic Oncology Translational Research Program at the Case Comprehensive Cancer Center in Cleveland, OH. The

Program, which included Case Western Reserve University, University Hospitals of Cleveland, and Cleveland Clinic, was a well-integrated, state-of-the-art research program with a rich repository of patient-derived cell lines and mouse ovarian cancer models that was highly useful for translational research and was perfectly poised to perform impactful translational research to uncover the drivers of ovarian cancer transformation and tumor recurrence. This program increased the interest in ovarian cancer research among the faculty. Most notably, the development of this program resulted in numerous collaborative projects and increased the ovarian cancer research endeavors on campus. Through these efforts in bringing awareness to ovarian cancer and developing a gynecological cancer translational research program, I was chosen as a Crain's Cleveland Business 40 Under 40 honoree.

In 2018, I was recruited to be an Associate Professor (with tenure) in the Department of Pathology and Obstetrics & Gynecology at the University of Michigan Medical School, to continue performing impactful research that through collaborative teamwork and rigorous research will improve the lives of women burdened by ovarian cancer. At the University of Michigan, I am the Director of the Michigan Ovarian Cancer Science and Innovation Consortium (MOSAIC), a statewide program that connects passionate physicians, scientists, and patient advocates from prestigious research institutions throughout Michigan. Its primary goal is to work together in order to perform impactful research that will uncover novel diagnostic tools or therapies that can ultimately improve the lives of all women diagnosed with ovarian cancer and advanced-stage uterine cancer. We currently have ~60 members from backgrounds in Public Health, Pathology, Cancer Biology, Genomics, Materials Science and Engineering, Biomedical Engineering, Bioinformatics, Gynecologic Oncology, Medicinal Chemistry, and Epigenetics. Through these programs, I have developed a state-of-the-art gynecologic tumor biobank, which includes novel

patient-derived cell lines, organoids, and mouse models, which are used to uncover advance personalized approaches to cancer treatment.

I am also the Associate Director of the Cancer Biology Graduate Program, a Member of the Rogel Cancer Center, the Biomedical Research Council (BMRC), Cancer Biology Graduate Program Steering Committee, and Elected Member of the Senate Assembly of the University of Michigan.

Beyond the aforementioned research, I serve on numerous international and national grant review committees, and I periodically review for more than 20 journals. I am also on the Editorial Board of the journal Endocrinology and am an Associate Editor for the Frontiers in Oncology (gynecological oncology journal). In addition, I serve as a key opinion leader for various biotechnology companies developing drugs to treat ovarian cancer. I serve on numerous grant review committees within my institution such as the institution's Biomedical Research Council (BMRC) for three years, where I evaluate University-wide prestigious limited submission awards. In addition, I am a member of the Rogel Cancer Center Research Committee (CRC), which evaluates all grants awarded by Rogel monthly. Nationally, I am a Charter Member of the Developmental Therapeutics study section at the National Cancer Institute (NCI), a Standing Member of the American Cancer Society's Mission Boost Panel, a Charter Member of the Cancer Center Pilot Grant Program at the Medical College of Wisconsin, and an ad hoc reviewer on various other national and international committees listed on my CV.

For a more detailed description of awards, grants, and publications, please refer to my complete curriculum vitae, which is attached as an appendix to this report. I am being compensated at the rate of \$775 an hour for the time spent on this work. I have never testified as an expert witness before.

II. SCOPE OF REPORT

This report reflects my analysis and opinions, based on my education, training and expertise as a cancer biologist, and a thorough review of the relevant literature, on the issue of whether cosmetic talc causes or contributes to the development of ovarian cancer.

Fortunately, many experimental tools have been developed to assess the impact of substances on the development of diseases, including cancer. Use of these tools, and independent review by experts, allow us to evaluate claims of causation.

In this report, I provide an overview of cancer, what is known about ovarian cancer, the origins of ovarian cancer, modeling malignant transformation, bioassays to assess neoplastic transformation, and an overview on inflammation. I then address my overall opinion on the hypothesized role of talc in ovarian cancer development and discuss numerous concerns with the data presented by Dr. Mandarino, Dr. Emi, Dr. Saed and their colleagues, and why the results of their research do not constitute scientifically sound evidence that cosmetic talc use can cause ovarian cancer.

III. SUMMARY OF OPINIONS

Based on my education and experience, I conclude that cosmetic talc, regardless of its exact constituents or alleged contaminants, does not cause or contribute to the development of ovarian cancer. Specifically, cosmetic talc has not been shown to be capable of migrating to the fimbrial ends of the fallopian tubes, from which most ovarian cancers arise. Nor has it been shown to induce any portion of the multistep malignant transformation process. The studies on which plaintiffs' experts rely have been performed on flawed cell lines, use physiologically irrelevant concentrations of talc, and, in any event, do not demonstrate neoplastic transformation.

IV. CANCER

Cancer is the most common human genetic disease. Cancer is caused by altered expression of genes or by genetic mutations – most often, a series of mutations, some of which may be inherited. Most cancers arise from several genetic mutations that accumulate in cells of the body over a person's lifespan. During division, every cell produces two identical progeny. Consequently, a cell that acquires a mutation transfers that mutation to its progeny via processes of cell division and growth. The proliferation of cells harboring cancer-associated mutations surpasses that of normal cells, thereby increasing the quantity of cellular candidates for further mutations. As cancer-causing mutations accumulate, they are replicated in descendant cells. If one cell finally acquires enough mutations to become cancerous, subsequent cancer cells will be derived from that one single transformed cell and a tumor will form. Because cells with cancer-linked mutations tend to proliferate more than normal cells, cellular candidates for additional mutations grow in number. Mutations continue to accumulate and are copied to descendant cells. These are called somatic mutations, and the genes involved are usually located on autosomes (non-sex chromosomes). Cancer may also have a germline mutation component, meaning that it occurs in germ cells, better known as the ovum or sperm. Germline mutations may occur de novo (for the first time) or be inherited from a parent's germ cells. Examples of germline mutations linked to cancer are the ones that occur in cancer susceptibility genes such as BRCA1 or BRCA2, which increase a person's risk for breast, ovarian, prostate, or pancreatic cancer.

Genes in which mutations cause cancer fall into two groups: tumor suppressor genes and oncogenes. Tumor suppressor genes prevent the development of tumors by: (1) regulating cell growth (preventing cells from dividing too quickly); and (2) controlling cell death (referred to by scientists as apoptosis). A mutation in these genes can cause cells to divide too quickly and fail to

die, resulting in cancer. Oncogenes similarly interfere with the normal growth and death of cells, enabling cells to proliferate uncontrollably and thereby leading to cancer. There are an estimated 10^{15} cell divisions during the lifetime of an adult. Replication errors alone result in thousands of new DNA mutations in the genome in every cell of the organism. However, the majority of those mutations are not in tumor suppressor genes or oncogenes. At least ~350 (1.6%) of the ~22,000 protein-coding genes in the human genome are reported to show recurrent somatic mutations in cancer with strong evidence that these contribute to cancer development.¹ Studies in mice have suggested that more than 3,000 genes, when appropriately altered, may have the potential to contribute to cancer development.² Mutations may be acquired while the cell lineage is phenotypically normal, reflecting both the intrinsic mutations acquired during cell division and the effects of exogenous mutagens such as tobacco use or UV light. During the development of the cancer, processes other than cell division, for example, DNA repair defects, may contribute to the mutational burden. When they are functioning properly, DNA repair genes help to fix damaged DNA. During the development of cancer, however, these genes can mutate, a process that causes other mutations in these cells, including chromosomal changes that promote cancer growth. Once cancer cells have acquired enough mutations, they gain additional attributes that distinguish them from normal cells in several ways: a) they grow indefinitely regardless of signals telling them to stop growing; b) they do not undergo programmed cell death (or apoptosis); c) they spread into surrounding tissue; d) they generate new blood vessel to supply nutrients to the growing tumor; e) they evade the immune system in order to not be attacked by immune cells; and f) they use different bodily energy sources from those that promote normal cell growth and thereby are able to grow faster than normal cells.

V. OVARIAN CANCER

Ovarian cancer is currently one of the deadliest cancers diagnosed in women. In 2024, there will be approximately 19,680 new cases and 12,740 ovarian cancer deaths in the US.³ The prognosis for patients diagnosed with ovarian cancer is grim, with overall survival rates remaining relatively unchanged for the past 30 years. The 5-year overall survival rate for all ovarian cancer patients is 49.1% and varies greatly with stage. Patients diagnosed with Stage 1 ovarian cancer have a 5-year survival rate of 92.6%, whereas those diagnosed with Stage 3/4 cancer have a 5-year survival rate of approximately 30%.³ The term “ovarian cancer” is a misnomer as it does not refer exclusively to cancer that originates from the ovaries.⁴ Rather, ovarian cancer is an umbrella term that refers to several different subtypes of cancer that can arise from different anatomical areas of the gynecological tract, including the ovaries, fallopian tube, and uterus.⁴ The World Health Organization currently separates ovarian cancer into three major types. The first type is epithelial ovarian cancer (EOC) which constitutes approximately 90% of all ovarian cancers. The second type is germ cell, which accounts for most of the remainder, and the third type is sex cord-stromal, which account for 3% and 2% of all ovarian cancers, respectively. EOC is further subdivided into 5 distinct subtypes based on cell type and grade. Each of the subtypes is distinct in terms of morphology, etiology, anatomic origin, molecular characteristics, and prognosis. Currently, a dualistic model exists for the classification of epithelial ovarian cancers into two groups, **Type 1** and **Type 2**. Type 1 EOCs include low-grade serous carcinoma (LGSC), low-grade endometrioid carcinoma (EC), mucinous carcinoma (MC), and clear cell carcinoma (CCC).⁵ Type 1 cancers make up 25% of the EOC cases, are usually considered low-grade, and are well differentiated. They tend to be driven by well-defined somatic mutations in KRAS, BRAF, PI3KCA, and ERBB2

genes and generally do not have p53 mutations. They typically progress slowly and are diagnosed at an early stage.⁵

Type 2 cancers include the high-grade serous carcinomas (HGSC), high-grade endometrioid carcinoma (HGEC), undifferentiated carcinomas, and carcinosarcomas. They make up the majority of the EOC cases and are normally characterized by a lack of consistent driver mutations, except for almost universal p53 mutations.⁵ They tend to exhibit a high degree of genomic instability and defects in the DNA damage repair (DDR) pathway.⁶ These cancers tend to be aggressive, highly metastatic, and are usually diagnosed at a late stage. HGSC makes up 75% of the serous carcinomas diagnosed and is responsible for the majority of deaths caused by EOC.⁵ The morphology of HGSC is characterized by poorly differentiated columnar cells that form papillae, solid masses, and slit-like spaces.^{6,7} They are positive for certain tissue markers, such as the mullerian marker PAX8, as well as the epithelial marker CK7, and the transcription factor WT1. HGSCs also stain positive for nuclear p53 due to accumulation of mutant p53. Genetically, HGSCs have very few mutations that are common among all patients, with p53 present in 96% of patients and BRCA1/BRCA2 mutations seen in ~20% of patients.^{6,7} However, most of the other mutations found in HGSC occur at a lower frequency. The most common genetic alteration in HGSCs is genomic instability, which is defined by frequent gains and losses of pieces of DNA.^{6,7} This is due in part to defects in the cell's ability to repair its DNA, which is called homologous recombination (HR) and DNA damage repair (DDR). Around 50% of all HGSCs have HR/DDR defects. HGSCs can be further categorized by gene expression patterns, which cluster into four distinct groups that are called immunoreactive, mesenchymal, proliferative, and differentiated based on the genes that they represent. Patients with the mesenchymal subtype of

HGSC tend to have the poorest prognosis and overall survival rates, although the exact reasons for this remain unclear.⁶

LGSCs are infrequent and make up about 10% of serous carcinomas and 2% of all ovarian cancers.^{3,5} They are typically diagnosed at a younger age, at early stage, are slow-growing, and have a much better prognosis and survival rate than HGSC. Morphologically, they are similar to HGSC, but they do not have nuclear atypia. LGSCs display similar immunophenotype markers as HGSC, including PAX8 and CK7.⁸ They generally do not have p53 mutation or aberrant p53 staining. LGSCs are genomically stable and have recurrent driver mutations in KRAS or BRAF that promote tumor progression.

Apart from the serous carcinomas, the other types of EOC occur infrequently. Endometrioid carcinomas (“EC”) account for the next-largest patient population, making up 10% of all ovarian cancers.³ These tumors usually arise from the endometrium, are associated with endometriosis, are typically diagnosed at early stage, are usually low-grade, and have a good prognosis. Morphologically, they are differentiated, with glandular structure similar to endometrial epithelium.³ The grade of EC can vary, with the low-grade showing very few defects in the nuclei and the high-grade showing significant defects. These tumors also have markers that can be used to define them further, such as being positive for PAX8 and CK7, negative for WT1 and possible overexpression of p53.^{3,8} Unlike HGSC tumors, ECs do not display a high degree of genomic instability, and they have a distinct molecular profile from HGSC tumors, accompanied by accumulation of mutations predicted to deregulate canonical Wnt signaling (usually *CTNNB1*), PI3K/Pten signaling (*PTEN*, *PIK3CA*), ARID1A, and PPP2R1A.^{5,61}

Although endometriosis is associated primarily with EC, it is also associated with increased risk for clear cell cancers (“CCC”) which account for 9.5% of all ovarian cancers and do not have

a well-defined site of origin.^{5,62} Twenty to fifty percent of women diagnosed with clear-cell and endometrioid ovarian carcinomas also have endometriosis.⁸¹ In women with endometriosis, the risk of developing clear-cell and endometrioid ovarian carcinomas is 3.4 and 2.3 times greater, respectively.⁸³ Patients with CCC are typically younger, tend to present at an early stage, and the most frequent and important specific gene alterations in CCC are mutations of ARID1A (~50% of cases) and PIK3CA (~50% cases).⁵ CCCs are associated with endometriosis and are aggressive with a poor prognosis, similar to HGSC. Morphologically they are large cuboidal or flattened clear cells that can grow in papillar, solid, or tubulocystic patterns.³ CCC genomic stability has not been well characterized. Immunologically, they are negative for PAX8, CK7, p53, and WT1, while they are positive for napsin A.^{3,8} Some recurrent mutations in ARID1A, PTEN, PIK3CA have been reported.⁶

Atypical endometriosis can also be associated with borderline tumors (BOTs)^{94,95} and has been observed in 10.5% of patients with borderline or invasive ovarian epithelial tumors.⁹⁶ BOTs are distinguished by the growth of cells and a little level of abnormality in the cell nuclei; therefore, they are also called tumors of low malignant potential. They account for 10% of all epithelial tumors. They manifest at an earlier age than carcinomas (median age, 45 years), have a potential hereditary risk and commonly have mutations in *KRAS* or *BRAF*.⁹⁷

Lastly, mucinous cancer (“MC”) accounts for only 3-4% of ovarian cancers,⁸ is usually low-grade, detected at early stage, and has a good prognosis. They are large, multicystic tumors that grow in papillary patterns. MC are usually positive for CK7 and PAX8, but not WT1 or p53. Recurrent driver mutations include *KRAS* (75%) and *HER2* (20%) activation.³

VI. OVARIAN CANCER RISK FACTORS

There are several risk factors that can contribute to the development of ovarian cancer. Certain genetic factors are associated with increased risk of developing ovarian cancer, and approximately 24% of ovarian cancers diagnosed have at least one predisposing germline mutation.⁹ Of these, mutations in BRCA1 and BRCA2 are the most common and make up about 18% of the germline mutations.⁹ The risk of developing ovarian cancer (as well as other types of cancer) is greatly increased in BRCA1/2 mutation carriers.^{6-7,9-13} The lifetime risk of developing ovarian cancer in BRCA1 carriers is 44% and 17% in BRCA2 carriers.⁴ However, BRCA1/2 carriers have increased sensitivity to therapies that affect DDR, such as platinum and PARP inhibitors, and thus have a better prognosis.¹¹ Other genetic factors for developing ovarian cancer are also usually components of DDR, and their inactivation contributes to increased DNA damage and tumorigenesis.¹⁴ There are at least 16 genes known to be involved in hereditary tumorigenesis, including TP53, ATM, RAD50, RAD51C, RAD51D, MRE11A, CHECK2, PALB2, BRIP1, and BARD1.^{9,13-15} This list of genes, as well as mutations within these genes, is constantly evolving as there are mutations that remain unknown, have an unclear impact on cancer progression or cannot be detected by current tests.¹⁶ For instance, though we may know some of the genes that predispose a woman to developing ovarian cancer, the exact mutations in those genes that cause cancer may not be clear; thus, they are referred to as variants of unknown significance (VUS).¹⁷ In a recent study that analyzed more than 800 patients who underwent genetic testing for *BRCA1/2*, 5.6% of the original VUS mutations were reclassified as pathogenic or likely pathogenic variants over a 13-year period.¹⁷ Further expanding the complexity of VUS mutations is another study that examined BRCA1 and BRCA2 intronic VUS mutations in a cohort of 707 ovarian cancer patients.⁸⁰ This study found that 2 mutations that were previously thought to be non-pathogenic

resulted in loss of protein expression and the mutations (BRCA1 c.4358-2A>G and BRCA2 c.475+5G>C) were reclassified as pathogenic variants.⁸⁰ Findings such as these highlight how germline genetic testing and classifying cancer-causing mutations is an evolving field.

Beyond new hereditary mutations being introduced in genes we already know to be involved in hereditary ovarian cancer, new genes continue to be identified. For example, Fierheller et al. uncovered a novel ovarian cancer-predisposing gene, FANCI, through whole genome sequencing of numerous families with ovarian cancer (OC) cases not harboring pathogenic mutations in either of the BRCA1 and BRCA2 genes.¹⁸ Women with congenital diseases such as Lynch syndrome (characterized by mutations in the genes of the mismatch repair pathway) also have an increased risk of developing ovarian cancer.

Repeated cycles of ovulation can contribute to the lifetime risk of ovarian cancer, and studies have shown that use of oral contraceptives can conversely reduce the risk of ovarian cancer. The explanation for this is not clearly delineated. Several earlier studies had postulated that it may be due to a reduction in the genotoxic and inflammatory stress associated with continuous follicular rupture and release. More recently, however, several studies have shown that the decreased risk may be due to the effects of increased progesterone on apoptosis.^{20,21} Reproductive factors, such as endometriosis or never carrying a pregnancy to term, can also contribute to ovarian cancer risk. Salpingectomy and oophorectomy are the most effective means of preventing ovarian cancer and are often recommended for high-risk patients, such as BRCA1/2 carriers, after childbearing is complete. Bilateral salpingo-oophorectomy can reduce the risk of developing ovarian cancer in such patients by approximately 70%, but not 100% given that ovarian cancer can originate from organs other than the fallopian tubes and ovaries, which are removed during bilateral salpingo-oophorectomy surgery.²² Other factors, such as environmental factors and

lifestyle choices, can also contribute to the risk of ovarian cancer. For example, obesity is associated with non-serous ovarian cancer,⁹⁸ and smoking has been shown to be associated with mucinous cancer.⁹⁹

Advanced age is also a risk factor for ovarian cancer, and patients are diagnosed at a median age of 63 years. Normal cell replications over the course of our lives contribute to the accumulation of random mutations that can eventually lead to cancer, hence the increasing risk with age.¹

There are currently two major barriers to successful treatment of HGSC that are the cause of the high mortality rate associated with HGSC. The first is that there are no reliable methods for early detection of HGSC, which results in more than 70% of HGSC patients being diagnosed with end-stage disease that has already metastasized throughout the peritoneal cavity. This is because initially ovarian cancer can be asymptomatic. When symptoms arise, they are often non-specific and may be mistaken for other diseases. Effective minimally invasive screening procedures, such as the mammogram in breast cancer or colonoscopy in colon cancer, are not feasible for HGSC early detection.

The second major barrier is that because such a high percentage of HGSC patients are diagnosed at end stage, there is a very high rate of recurrence (>80%). Both barriers translate into a poor prognosis, and both have their roots in the fact that the origins and natural history of HGSC are still poorly understood. Unlike most other epithelial cancers, the anatomical complexity and location associated with HGSC has made understanding the HGSC tumorigenesis process extremely difficult.

VII. INFLAMMATION

Inflammation is a critical defense mechanism that is essential to health. It contributes to numerous physiological and pathological processes within the human body, such as wound healing and infection.⁶³ The inflammatory cascade represents an immune response of the host to damaging stimuli and contributes to rebuilding tissue homeostasis in order to resolve acute inflammation.⁶⁴ The etiologies of inflammation can be infectious, such as bacteria and viruses, or non-infectious, such as chemicals or tissue damage. Beyond the role of inflammation in normal physiology, in the last couple of decades, it has been shown that inflammation can contribute to the development and progression of certain cancers. One reason is that tumors that emit persistent oncogene stress signals chronically induce inflammatory cell recruitment, which aids in their survival.⁶⁵ Thus, some cancers are thought to be caused by infection, chronic inflammation or autoimmunity at the same tissue or organ site.⁶⁶ In most of these cases, it is due to pathogenic diseases such as inflammatory bowel diseases (IBD), chronic hepatitis, *Helicobacter*-induced gastritis or *Schistosoma*-induced bladder inflammation, increasing the risk of colitis-associated cancer (CAC) (though only 2% of CAC cases are preceded by intestinal inflammation), liver cancer, stomach cancer or bladder cancer, respectively. Overall, however, the development of the large majority of cancers is not preceded by chronic inflammation.⁶⁷

Inflammation does not appear to play a role in ovarian cancer. Although the surface epithelium of the ovary and the fimbriae of the fallopian tube are consistently exposed to strong inflammatory stimuli due to natural by-products of ovulation, follicular fluid, and ovulatory rupture, the role of chronic inflammation in driving OC development has not been demonstrated. This suggests that the cells in this microenvironment have adapted to withstand these pro-inflammatory insults throughout their life. To date, there is no evidence that inflammation

precedes HGSC and there is no evidence of an association between chronic inflammation and the occurrence of the precursor's lesions of HGSC.¹⁰⁰

VIII. MALIGNANT TRANSFORMATION

Understanding the mechanisms that underlie cancer development requires knowledge of cellular transformations; in the next section, I will delineate the defining characteristics of transformation as well as the fundamental signaling events that initiate the process. Malignant, or oncogenic, transformation is a complex, multi-step process in which normal cells undergo a slow conversion as oncogenic and tumor suppressor signaling compete for dominance.²³ While the exact sequence and steps necessary for complete transformation of normal cells varies depending on the cancer, there are certain general signaling events necessary for transformation to occur. Full malignant transformation requires changes that: 1) alter telomere maintenance to bypass replicative senescence; 2) inactivate tumor suppressive pathways; and 3) activate oncogenic signaling pathways.²³ After a finite number of cell divisions, normal cells will undergo replicative senescence. In cancer cells, this process is bypassed by upregulation of the hTERT catalytic subunit of human telomerase. Loss of tumor suppressor signaling typically occurs through functional inactivation of the p53/Rb signaling pathways, facilitating cell cycle deregulation and loss of ability to undergo apoptosis. Various pro-oncogenic signaling events, such as Ras activation and upregulation of c-MYC, facilitate increased proliferation, angiogenesis, and metastasis. The combination of these three oncogenic components provides the necessary changes for complete transformation from normal cells to premalignant lesions to fully transformed carcinomas. Progression of a normal cell to a neoplastic cell capable of forming a tumor happens because of random mutations and epigenetic alterations that affect genes controlling cell survival, proliferation, metastasis and other traits associated with the malignant phenotype. These

alterations occur in the context of complex microenvironmental inputs, which exert selective pressures (either positive or negative) on the evolution of the developing cancer cell. Oncogenic transformation normally requires at least two to three oncogenic “hits” or molecular alterations that promote the malignant phenotype. In human cells, more than two hits (as many as 10) are usually required for progression to fully developed carcinoma depending on the cancer type.⁸¹ The “hits” necessary for successful oncogenic transformation usually consist of gains of oncogenes and loss of tumor suppressors.

An oncogene is a gene that contributes to the development of the malignant phenotype. This is often accomplished by activation of a proto-oncogene, which has a controlled role in normal cell growth and division. Aberrant activation of a proto-oncogene (i.e., mutation, transcriptional activation, post-translational modification, epigenetic activation, etc.) converts it to an oncogene, which then promotes tumorigenesis. Tumor suppressors are the other primary category of regulators involved in tumorigenesis. Tumor suppressors are genes that prevent uncontrolled cell growth and proliferation in response to oncogenic stimuli. They can do this by promoting cell cycle arrest, senescence, and apoptosis. Loss of tumor suppressor function (via mutational inactivation, decrease in expression, inhibition of function, etc.) also promotes tumorigenesis.

Human cells are highly resistant to oncogenic transformation, and several barriers must be overcome for a normal cell to transform into a cancer cell. Normal cells typically have a finite lifespan (termed the Hayflick limit) or number of cell divisions that they can undergo before they stop dividing. The normal machinery of the cell tightly regulates the signaling involved in cell division to prevent excessive or aberrant cell proliferation. To escape this regulation, one of the major barriers that cells must overcome is replicative senescence. As cells reach the end of their replicative lifespan, they are genetically programmed to undergo a process termed replicative

senescence or M1. This is usually facilitated through increased activation of p53 and RB1 signaling, which prevent cell cycle progression, promote cell cycle arrest, and activate apoptosis. These signaling pathways can be activated by several cues, including reaching the Hayflick limit, DNA damage, increased reactive oxygen species, increased stress signaling, strong mitogenic signaling, and oncogene activation. Inactivation of the p53 and RB1 signaling pathways is needed for the cell to continue dividing past this limit. Loss of RB1 function removes the block on G1/S cell cycle progression, and loss of p53 function promotes cell cycle progression and inhibits apoptosis. This allows the cell to continue dividing due to loss of cell cycle regulation. Eventually, the cell will reach a point where the telomeres (structures at the end of chromosomes that protect the DNA) become critically shortened. This is called M2 or “crisis.” In the presence of a competent p53 pathway, these critically short telomeres facilitate large-scale genomic instability, which can result in necessary cell death. This is because extremely short human telomeres cause decrease in growth by either activating the tumor suppressor gene p53 or starting the p16/RB pathway. Cancer cells also need to avoid the tumor suppressor signaling that comes with having shorter telomeres. Cell immortalization – one of several steps toward carcinogenesis – usually happens because of activation of hTERT, the catalytic subunit of telomerase. Indeed, hTERT activation is seen in the overwhelming majority of human cancers. hTERT activation leads to increased telomerase activity, which maintains the telomeres, prevents the activation of tumor suppressor genes, and allows the cells to continue dividing indefinitely. At this point, the cells are immortal but still may not be capable of forming a tumor. In vivo, this is akin to a pre-malignant lesion, which shows some of the characteristics of a fully developed carcinoma, such as loss of contact inhibition and dysplasia, but is limited in terms of growth and metastasis. Further oncogenic alterations such as increased proliferative signaling (via increased activity of oncogenes

such as MYC or RAS) and increased epithelial-to-mesenchymal transition (EMT) are needed to promote the transition of the pre-malignant lesion to carcinoma in-situ. Even after cells begin to proliferate abnormally, additional genetic mutations are required to transform them into cells that will metastasize into other tissues, the characteristic property of metastatic carcinoma.

IX. EXPERIMENTAL MODELS TO ASSESS MALIGNANT TRANSFORMATION

Modeling carcinogenesis and determining whether a chemical or genetic alteration can induce onco-transformation are essential to understanding the factors that drive tumor development. Therefore, numerous cell-based and animal studies have been done to measure the acquisition of a malignant phenotype. Tumor formation usually happens over a period of decades and normal human cells do not grow on plastic (e.g., petri dishes) indefinitely. Therefore, the most critical first step in an in vitro experiment is determining the “normal” cells that will be used for the assays. Typically, normal fibroblast cells that can already grow on plastic plates indeterminately are used because they have been immortalized via activation of hTERT and loss of several key tumor suppressor genes. Unfortunately, these cells are not biologically relevant for most cancers given that very few cancers originate from fibroblasts. Therefore, it is best to use normal cells that are known to be the precursor for the specific cancer. For example, in order to assess whether a substance can induce HGSC or EC malignant transformation, it is essential to use normal fallopian tube secretory epithelial cells (FTSEC) or endometrium cells respectively since HGSC usually arises from the fimbriae of the fallopian tubes and endometrial cancer in the endometrium. Recent work from our laboratory details the use of three different FTSEC cell line models to reveal the transformative ability of the oncogenic microRNA, miR-181a.²⁴ Figure 1A shows pictures of one of the normal FTSEC models used with cells that have been immortalized using hTERT, have TP53 loss and have a CDK4 mutation, therefore mimicking a serous tubal

intraepithelial carcinoma (STIC) lesion, and highlights the morphological changes induced by expressing one (miR-181a) or two (miR-181a + MYC) oncogenes, as well as the distinct growth patterns. Given that transformation is a multi-step process, several other assays are required to confirm a malignant phenotype, including, but not limited to, increased proliferation (Figure 1B), increased anchorage-independent growth or sphere formation (Figure 1C), and most importantly, growth of these cells in immunodeficient mice to confirm that they can grow tumors (Figure 1D).²⁴ Additional comprehensive molecular profiling of the transformed cells should also be performed to confirm consistent genetic signatures with human tumors. Ultimately, Figure 1 briefly provides a description of what is commonly accepted for ascertaining the transformative ability of various potentially carcinogenic genetic alterations or chemicals. Some studies have concluded that there is a satisfactory predictive capability of using sphere assays to test for malignant transformation; however, the assays were not validated in vivo and did not correlate with tumor formation in mice. Thus, the Organization for Economic Cooperation and Development (OECD) did not consider it to be sufficiently robust for regulatory test guideline purposes.²⁵⁻²⁷

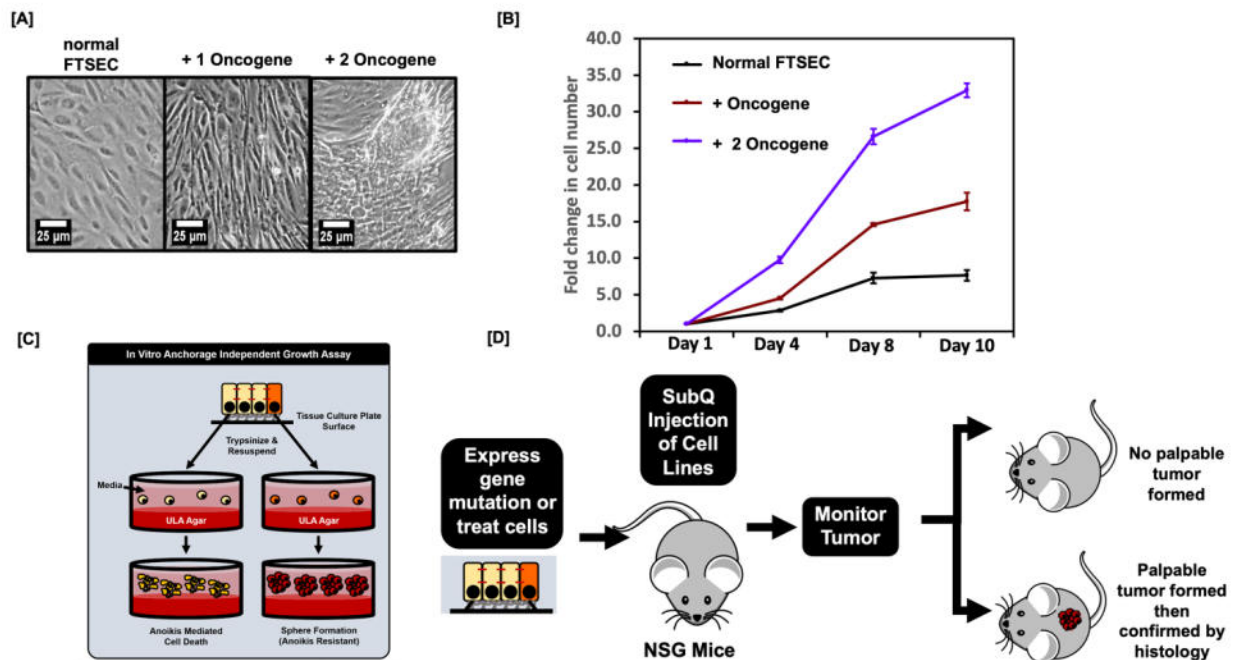


Figure 1. Bioassays to test malignant transformation. **A.** Normal fallopian tube secretory cells (FTSEC) are immortalized via the activation of hTERT and inactivation of TP53 to allow them to grow on plastic indefinitely. To test whether certain genes can contribute to malignant transformation they can be overexpressed in the cells either alone or in combination and observed over time to assess changes in morphology. **B.** Overexpression of one or both oncogenes result in increased cell growth whereas the normal cells stop growing at day 8. **C.** Another assay commonly performed is sphere-forming assay in soft-agar to measure anchorage independent growth given that normal cells cannot grow in suspension or in spheres. **D.** The most critical step of transformation is determining whether the cells that have been modified can grow tumors in mice.

X. ONCOGENIC TRANSFORMATION OF OVARIAN CANCER

High Grade Serous Ovarian Cancer

The lack of knowledge about the natural history of HGSC has made it difficult to develop effective early detection and intervention strategies or novel therapeutic approaches. However, over the past 10 years, progress has been made in elucidating the origins of HGSC. For the last three decades, the predominant view was that HGSC originated from the ovarian surface epithelium (OSE). The OSE model was initially proposed by Fathalla in 1971 and was termed the “incessant ovulation” hypothesis.²⁸ This model of HGSC tumorigenesis posited that the process

of incessant ovulation subjected the OSE to repeated cycles of rupture and repair. The continuous process of repeated ovulation was thought to promote a pro-inflammatory microenvironment and chronic DNA damage in the OSE that facilitated its transformation. Follicular rupture facilitates a spike in ROS and pro-inflammatory cytokines, which increases the genotoxic stress the OSE cells are under, making them more susceptible to mutation and oncogenic transformation. This hypothesis was initially based on the observation that oral contraceptives (which prevent ovulation) reduce the risk of developing HGSC, the primary tumor mass was located on the ovary in the majority of HGSC patients, and later the observation that women with germline BRCA1/2 mutations (and therefore defective DDR) had a greater risk of developing HGSC. Initially, it was thought that OSE inclusion cysts exposed to the interior ovarian follicular matrix, would undergo metaplasia and eventual transformation. However, there is a high frequency of inclusion cysts in pathologically normal ovaries. In addition, there is no definitive evidence of inclusion cyst precursors that give rise to HGSC, or that OSE cells in the inclusion cysts can undergo müllerian transdifferentiation and metaplasia, which are forms of cellular transformation.

The proposal that the OSE was the site of origin for HGSC offered almost no insight into the details of how HGSC developed. The natural history of HGSC languished in obscurity for more than 20 years until by serendipity an alternative site of origin was uncovered. The discovery that women who carried the germline BRCA1/2 mutation were at high risk of developing ovarian cancer led to the regular employment of prophylactic risk-reducing bilateral salpingo-oophorectomy (RRSO) (surgical removal of the fallopian tubes and ovaries). RRSO allowed pathologists to meticulously examine the fallopian tube and ovaries of these high-risk patients for occult cancer lesions.

Interestingly, no ovarian lesions were uncovered, but several in-situ and invasive lesions were discovered in the fallopian tube surface epithelium (FTSE).²⁹ Follow-up studies confirmed these observations, with occult lesions being present in the FTSE (usually concentrated at the fimbriated end) in 40-100% of patients. These lesions were also present in the FTSE of women who were not BRCA1/2 carriers, and not at elevated risk for developing HGSC.²⁹⁻⁴²

Following the initial studies, Nik N et al. proposed that the occult tubal cancers might shed metastatic cells from the fallopian tube that could seed and then grow on the ovary.⁴³ This

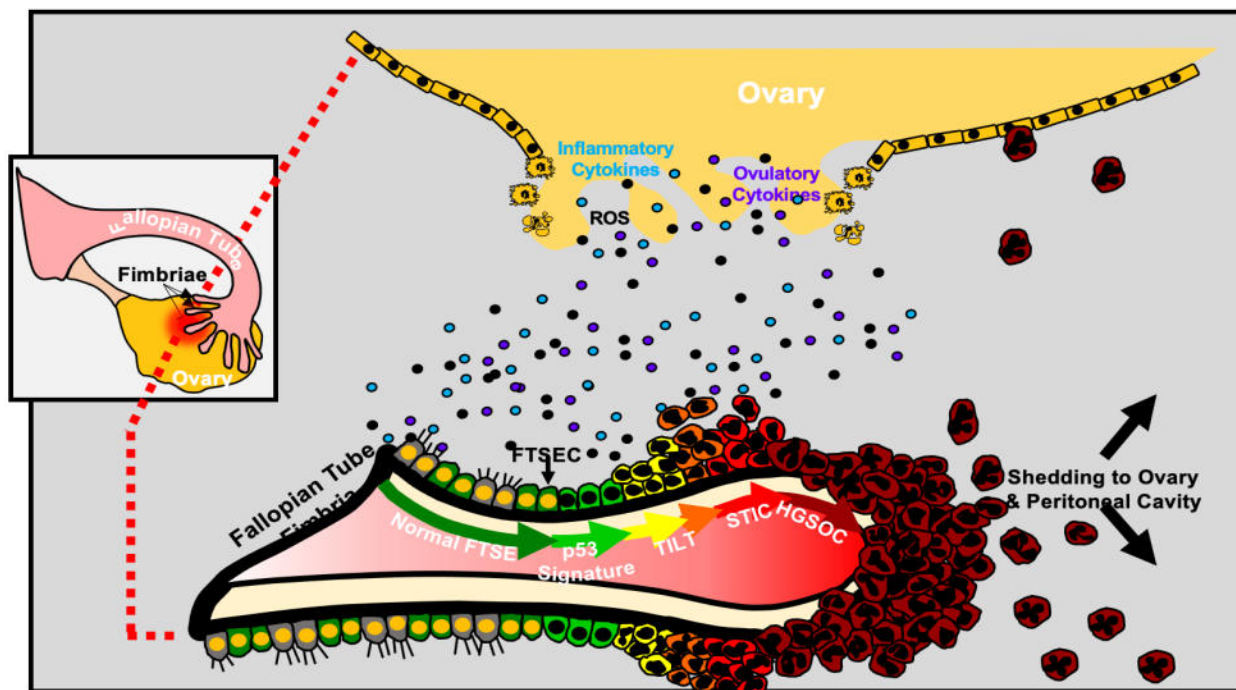


Figure 2: Incessant ovulation has been deemed one of the factors that contributes to HGSC carcinogenesis because of consistent observations that the number of lifetime ovulations is positively related to ovarian cancer incidence. The fluid ruptured from follicles during ovulation is proposed to be carcinogenic because it contains abundant reactive oxygen radical species, which can damage DNA, break DNA strands, and initiate DNA damage repair. The fallopian tube epithelial cells, especially those located at the fimbriated ends where most of the STICs are found, are directly exposed to follicular fluids immediately after ovulation. With repeated episodes of DNA damage and repair, the follicular fluid-exposed tubal epithelial (putative progenitor) cells may acquire somatic mutations, some of which are cancer-promoting, and clonally expand. This carcinogenic process accelerates in the presence of germline mutations and epigenetic inactivation of genes participating in homologous recombination DNA repair such as BRCA1 and BRCA2. Furthermore, various growth factors in follicular fluid promote the transformation of TP53 -mutated epithelial cells. The STIC then undergoes malignant transformation and sheds to various other sites, including the ovary, throughout the peritoneal cavity.

hypothesis formed the basis for the FTSE or Tubal theory of HGSC carcinogenesis (outlined in Figure 2). The occult carcinoma in situ found in the fallopian tube was named STIC and was proposed as a precursor of HGSC.

STICs have a high nuclear to cytoplasmic ratio, nuclear pleomorphism, lack of ciliated cells, sporadic mitotic figures, and loss of epithelial polarity. STICs are present in approximately 60% of HGSC patients, 8-10% of healthy BRCA1/2 carriers, and 1-3% of the healthy population.⁴⁴⁻⁴⁵

In addition to STIC, other precursor lesions originating from the FTSE have also been identified. The first was a pre-malignant lesion termed the “p53 signature” (PSIG). The PSIG is a stretch of 12-30 morphologically normal-looking FTSE cells that stain strongly for nuclear p53 (indicating p53 mutation). PSIGs are not proliferative, but do show increased staining of γ H2AX foci, indicating an increase in DNA damage in these cells compared to the surrounding normal cells.⁴⁶ PSIGs can be found in 50% of salpingectomies from all women (healthy and HGSC patients) and are found at similar frequencies in BRCA1/2 carriers and non-BRCA1/2 carriers.⁴⁷ PSIGs are usually concentrated at the fimbrial end of the fallopian tube and occur at a higher frequency in conjunction with co-occurring STIC. Often, the PSIGs are seen in histological continuity with STIC, suggesting a clonal origin.

Based on the pathological studies of occult lesions in the fallopian tube, a histological model of HGSC pathogenesis from the fallopian tube has emerged.⁴⁸ In this model, there are two normal cell types present in the FTSE. The first are FTSECs, which secrete a variety of factors that facilitate oocyte survival and fertilization. The second are fallopian tube epithelial ciliated cells (FTCs), which facilitate transport of the oocyte from the proximal to distal end of the fallopian tube. FTSECs are proposed as the cell-of-origin for HGSC as they are the only cell type of the

two that can be transformed in vitro and in vivo. FTSECs subjected to the transforming environment of the juxtaovarian niche undergo p53 mutation to become PSIG cells, which are the earliest detectable HGSC precursor lesion. PSIGs then undergo yet undefined further oncogenic alterations, which promote their transitional oncogenic transformation to STIC. The STIC then undergoes epithelial-to-mesenchymal transition (very generally, the cells become mobile) and sheds or spreads to various other sites, including the ovary and throughout the peritoneal cavity.⁴⁸

The evidence to support a tubal origin of many (if not all) HGSCs is substantial. FTSECs isolated from human fallopian tube fimbria can be transformed to give rise to tumors that are histologically and genetically similar to HGSC using viral and non-viral methods.⁴⁹⁻⁵¹ STICs are associated with the majority of HGSCs diagnosed and bear a high degree of genetic and morphologic similarity to HGSC. Additionally, no equivalents of STICs or PSIGs have been found in the ovary during prophylactic risk reduction surgery (RRSO) regardless of BRCA status. STICs have an increase in expression of oncogenes such as CCNE1 that are also upregulated in HGSC. STICs can also be found in prophylactic RRSOs where no carcinoma is present (refuting the contention that STICs are only metastases to the fallopian tube rather than the initiating lesion). STIC cells also have shortened telomeres compared to HGSC. Comparative gene expression profiling and phylogenetic analysis of OSE, FTSE, and HGSC show that HGSCs are more closely related to FTSE than OSE.^{50,51} Several genetically engineered mouse models of HGSC also support a tubal origin for the majority of HGSCs.⁵²⁻⁵⁴ The first HGSC genetically engineered mouse model used an AMHR2-Cre-driven model to investigate HGSC pathogenesis. AMHR2 is a semi-specific mullerian promoter expressed in the FTSE. Kim et al. used AMHR2-Cre-driven deletion of Dicer and PTEN to generate tumors that had some similarities to HGSC, which did not form when the fallopian tubes were surgically removed.⁵²

An improved genetically engineered mouse model was then developed by Perets et al. that utilized the mullerian-specific PAX8 transcription factor to drive Cre expression.⁵³ The PAX8-Cre model was much more specific for conditional expression of Cre in the fallopian tube and specifically FTSECs. Different combinations of clinically relevant oncogenic alterations, including PTEN deletion, p53 deletion, and BRCA1/2 deletion in the PAX8-Cre mice resulted in tumors that recapitulated the morphology, precursor lesions, genetics, markers, and dissemination of HGSC to a high degree. In addition, they showed that mice with salpingectomy did not form tumors while those with either hysterectomy or oophorectomy did.⁵³

Lastly, a third genetically engineered mouse model has been developed using the mouse mullerian-specific OVGP1 promoter to drive Cre expression. In the mouse, OVGP1 is expressed 45 times higher in the fallopian tube and FTSECs than in any other female reproductive tissue. The OVGP1-Cre mouse model most faithfully recapitulates HGSC in humans and is the closest mimic to what is believed to happen during human HGSC pathogenesis.^{54,55}

XI. COSMETIC TALC AND OVARIAN CANCER

A. Lack Of Evidence Showing That Talc Increases Ovarian Cancer Incidence.

Numerous carcinogenesis bioassays have been performed in animals to assess whether talc can induce tumor development, and none of them has shown an increase in ovarian cancer. For example, using female Sprague-Dawley rats that received direct intrabursal (adjacent to the ovary) injection of 100 mg/mL Italian talc, histological examination at 12 months showed some changes in some of the treated animals but no evidence of ovarian neoplasia (or nuclear atypia) in any animals.⁶⁸ In another study, 100-mg of USP-grade talc was intraperitoneally or intravaginally applied and observed for 18 to 21 months, and no tumors were found on the ovaries or FT.⁶⁹ Lastly, in 2009, Keskin et al. showed that when talc was delivered to rats intravaginally or via their perineum, no neoplastic changes were detected even though they observed foreign body reactions

in both control and talc treated groups.⁷⁰ The authors concluded that direct intravaginal or intraperitoneal talc application may have “unfavorable effects” like foreign body reaction, but did not cause “neoplastic change.” In sum, these studies conclude that direct injection of very high doses of talc may cause foreign body reaction and/or infection, but not cancer, in animals.

B. Talc Particles Cannot Travel To The Fallopian Tubes, Precursor Lesions, Or Ovaries.

Several studies have attempted to demonstrate that talc can migrate through the female genital tract to the ovaries and peritoneal cavity. However, these studies were conducted under artificial conditions that do not mimic the use or perineal application of cosmetic talc, and do not conclusively show that talc can migrate to the fallopian tubes or ovaries.⁷³⁻⁷⁵

Numerous animal studies have been performed to assess whether talc particles can migrate through the gynecological tract and none has shown that particles can translocate from the vagina to the ovaries or fallopian tube (FT). It would be hard to comprehend how cosmetic talc could allegedly initiate HGSC if it cannot migrate to the fimbrial end of the FT. Henderson et al. (1986) placed 100 mg/mL of talc particles in 250 uL of phosphate into the vagina of Sprague-Dawley rats and found no talc particles in the ovaries of the animals after 48 hours.⁷⁶ In addition, several other studies show similar results, including one performed in cynomolgus monkeys (*Macaca fascicularis*), whose anatomy is much closer than rats to humans. Monkeys received 125 mg of neutron-activated cosmetic talc suspended in 0.3 mL of deionized water. None of the monkeys had translocation of talc into the oviducts despite artificial conditions that would be much more likely to promote migration than application to the external genitals.⁷⁷ As a way to keep the monkeys from moving, a Velcro strap was used to hold their pelvises up and their knees bent close to their chests. The monkeys were then given an injection of the man-made talc powder into the vaginal fornix (the part nearest the cervix). The monkeys were given 10 units of oxytocin once a

week to make their uteruses contract, further promoting the possibility of retrograde migration. This was done 30 times on each monkey. Perineal washing was done two days after the 30th talc injection into the back of the vaginal fornix and ultimately even in these non-physiological conditions it was concluded that there were no detectable amounts of talc moving from the cynomolgus monkey's vaginal fornix to the uterus or elsewhere. Lastly, in a National Toxicology Program (NTP) study where female rats were covered with talc so that there was ample opportunity for oral, respiratory, and perineal exposure, talc particles were identified in the lungs of exposed rats but were not found in the fallopian tube, ovaries, or ovarian bursa of any of the rats.⁷⁸ From all these studies, there is no evidence that talc has been found on the fallopian tubes of any animals, undermining the theorized role of cosmetic talc in the development of high-grade serous ovarian cancer.

C. Cosmetic Talc Does Not Induce Malignant Transformation.

Several bioassays outlined in Section IV above can be used to assess the role of a gene's or chemical's impact on malignant transformation. However, to date, there have been no studies that have demonstrated that cosmetic talc induces neoplastic transformation.

Buz'zard. In 2007, Buz'zard et al. claimed that talc induced cellular transformation of "normal" ovarian epithelial cells and a granulosa cell line while also promoting cell proliferation and increased reactive oxygen species in cell culture.⁷¹ There were many flaws with this study, and the results do not justify these conclusions. For example, the cells that were used for the studies were not appropriate given that fallopian tube cells are the precursor cells for HGSC and the granulosa cells used (which come from the ovaries, not the fallopian tubes) are not appropriate for studying epithelial ovarian cancer. In addition, when performing colony formation assays, it is standard to show a representative image of the colonies that form in order for the reviewer to

appreciate the difference in the number and sizes of the colonies between the experimental groups. Buz'zard failed to do so. The cell viability data also do not match what would be expected from a transformed cell (as shown in Figure 1 of this report) because the data show that talc increases viability at low doses but kills them at higher levels. The authors also say that adding 5ug/mL of talc increases viability at early timepoints. This should be accompanied by continued growth increases over time, but this is not seen and the viability actually decreases.

At the highest level of talc treatment, two different ovarian cells showed statistically significant *decreases* in viability compared to untreated controls – the opposite of what would be seen if talc were actually causing carcinogenesis. In any event, even if Buz'zard had shown increased cell viability, cellular transformation is a multi-step process. Buz'zard and colleagues used just one assay (growth of cells in soft agar), which is not sufficient to claim neoplastic transformation, as highlighted in Section VIII. Finally, the authors looked into what talc does to the production of reactive oxygen species (ROS) in cells and found that it decreases and then increases a little over time (again, a result that is hard to explain and inconsistent with a dose-response). Because the effects on ROS production are small, these results probably are not biologically meaningful. After all, the positive control H₂O₂ caused the OSE cells to make 2.5 times more ROS. The authors also show that increasing quantities of talc cause ROS to be released in polymorphonuclear neutrophils (PMN). However, this is only when compared to controls that were not treated, and it does not consider the vehicle in which talc was resuspended, which is likely to be contributing to cell death, thereby leading to ROS.

Ultimately, the results in this paper fail to demonstrate that cosmetic talc causes ROS production or transforms ovarian cells.

A few more recent studies have examined the effects of talc on cells such as macrophages on ovarian cancer cell growth to ascertain the hypothesized impact of talc on transformation.^{89,90} Tumor-associated macrophages (TAMs) are often present in large numbers in the ovarian cancer tumor microenvironments (TMEs). In particular, TAMs can make up a high percentage of the cells in peritoneal tumors and ascites.¹⁰¹ However, whether macrophages contribute directly to the initiation of OC or influence early transformation has not been shown; therefore, the clinical relevance of these studies is unclear. In addition, because macrophages can function to stimulate the immune system or to suppress it, they can be either tumor-promoting or tumor-suppressing. For instance, a significant presence of macrophages in solid tumors, such as breast cancer, bladder cancer, melanoma, and prostate cancer, is frequently linked to a poor prognosis or tumor progression. Conversely, in colorectal and stomach cancer, a significant presence of macrophages is associated with a more favorable outlook.¹⁰² The contradictory effects that have been observed have been associated with the ability of macrophages to alter their activation state in response to environmental factors, as determined by the genes they express. This highlights the importance of utilizing the appropriate models and experimental conditions to best reflect human disease. As described more fully below, these investigations are deficient in the rigor, appropriate models, and clinical applicability required to validate the assertion that cosmetic talc is a contributor to the development of ovarian cancer.

Mandarino. This paper sought to evaluate the effect of (industrial-grade) talc alone or in combination with 17- β estradiol (E2) on macrophages by evaluating cytotoxicity, gene expression, and viability of mouse ID8 cells in co-culture with mouse macrophages. The authors claim that their “findings suggest that in vitro exposure to talc, particularly in a high-estrogen environment, may compromise immunosurveillance functions of macrophages.”⁸⁹ This conclusion would be of

limited clinical relevance if it accurately reflected the results of the study, and there is reason to question that the results support that conclusion.

First, the cell lines used are not relevant. As noted above, it is not clear that macrophages play a role in OC initiation and progression. Even assuming there is a role, though, the study used macrophage cell lines rather than primary macrophages (i.e., it did not use macrophages obtained directly from living mice). Given the different impacts that were observed in gene expression among the various cell lines used in this study (as discussed below), it would be speculative to suggest that the results observed in any one of these cell lines accurately describes what would occur in the macrophages that would serve any proposed role in OC. In addition, one of the macrophage cell lines used for some of the studies, IC21 cells, are genetically male; this calls into question the interpretation and relevance of any estrogen-dependent effect. Furthermore, the authors' use of a mouse ovarian cancer cell line (ID8), which the authors incorrectly classify as mouse ovarian epithelial cells throughout the manuscript, further limits the paper. Due to the transformation that these ID8 cells have already undergone, it is no longer feasible to evaluate the progression of malignancy. And ID8 cells are not even a good model of early ovarian cancer since they derive from the ovaries themselves, not from the fallopian tubes in which most OC cases arise. Furthermore, it has been demonstrated that this cell line does not resemble the known subtypes of human ovarian cancer (for instance, it does not contain mutations characteristic of ovarian cancer subtypes), thus rendering the clinical applicability of the studies questionable.⁸⁴ For these reasons, Mandarino et al. provides no evidence that cosmetic talc can cause or contribute to transformation.

Second, Mandarino et al. reported their "key finding" (i.e., the supposed effect of talc and E2 on proliferation of cancer cells in co-culture with macrophages) using a hybrid metric that

obscures what is occurring in the study. In order to study proliferation, which is the number of times a cell divides, the authors transduced the ID8 cells with a vector that expresses GFP (i.e., a fluorescent protein) driven by the *EF1a* promoter, which allowed the authors to characterize the number of ID8 cells via flow cytometry. However, given that they are using a surrogate biomarker (i.e., the number of cells exhibiting GFP expression) rather than reporting the actual number of surviving ID8 cells, it is important to determine whether E2 itself effects GFP expression. This is important because the authors do not report the percentage or number of cells that express GFP (i.e., the number of ID8 cells in a given population); rather, they fold that number into a combined metric that is also driven by the mean intensity of the fluorescence. Therefore, an increase in the hybrid measure could be driven by increased GFP expression (which would not be relevant to ovarian cancer) rather than by reduced macrophage activity and/or increased OC cell number, particularly given how modest the effect was when such high concentrations of E2 (2 ug/mL) were used. When the authors investigate the correlation between cell number and fluorescence detection of ID8-GFP⁺ cells in Supplementary Figure 1, they omit an ID8-GFP⁺ control lacking E2. This omitted control would have provided confirmation whether the cell number did indeed increase, rather than merely the amount of GFP expressed by each cell. Furthermore, Supplementary Figure 3, in which the experiment was validated in cells without the GFP transgene, shows that there was no difference between the effect of talc alone and talc in combination with E2.

Third, the study showed only modest effects even at doses of E2 that are not physiologically relevant. It is important to perform experiments using E2 concentrations found in the ovary microenvironment if the investigators want to evaluate the effects of talc and E2 on development of ovarian cancer. Previous studies have demonstrated that E2 concentrations in the follicular fluid of pre-menopausal women typically range from 24 to 621 ng/mL, which are significantly lower

than what is used in these studies.⁸⁵ The authors of Mandarino et al. seem to agree, writing that E2 serum levels can rise into the “ng/mL” range (citing papers that reported on mice) and that “ovarian tissue concentration of E2 is more than 100-fold higher than in serum” based on a paper⁸⁶ that found that estradiol levels were lower in the setting of ovarian cancer (and thus would not be expected to reach the “ng/mL” levels that Mandarino et al. cite as the high end of the range for “normal” mice and humans). Moreover, more than 65% of patients diagnosed with ovarian cancer are postmenopausal⁸⁷ and have reduced estrogen (as the study cited by Mandarino et al. confirms). However, E2 was used in doses of up to 10 ug/mL in Mandarino et al., which is equivalent to 10,000 ng/mL. Mandarino et al. used 2 ug/mL (2,000 ng/mL) – substantially higher than what would be expected in tissues of even pre-menopausal women – in what they described as their “key finding.” This is critical, because Mandarino et al.’s “key finding” (as shown in Figure 8 of the article) was supposedly inhibited tumoricidal activity after co-incubation of fluorescent ID8 GFP+ cells with phagocytes pre-treated with talc and E2. However, the experiment was performed with 10 ug/well of talc and 2 ug/mL of E2, and even at those concentrations, it showed only about a 0.5% increase in the above-described hybrid measure when comparing talc and control cells without E2 present, and only a 1% increase in the presence of E2 (which was not markedly different whether chromosomally female or male macrophages were assessed).

In short, the similarity in behavior between the female and male macrophages calls into question how and whether the effects observed were driven by E2 exposure. Moreover, the study employed talc in concentrations of up to 20 ug/well in Mandarino et al. It is not at all clear that this represents a physiologically possible concentration, and the rationale for using these doses is not provided. The minimal increase in Mandarino et al.’s hybrid metric at these doses is not relevant to ovarian cancer. It is noteworthy that a similar assessment was made by the editor of

Particle and Fibre Toxicology, who opined that the research was “too preliminary to conclude that talc combined with oestrogens affects the immunosurveillance of ovarian cancer cells.”¹ And the authors themselves acknowledged that they “did not investigate the carcinogenic properties of talc per se.”

The authors’ evaluation of gene expression in phagocytes exposed to talc is likewise problematic. Although the authors observed alterations in gene expression within the macrophages in the study, the data were merely descriptive. The biological effects of these genetic alterations have not been validated. For instance, the extent to which each gene is modified or whether this modification leads to a difference in protein expression, or secretion of the protein, is crucial. Without the validation of the gene expression changes, the potential impact of the observed gene changes on the macrophages’ function and, most importantly, its effects on ovarian cancer cells, remain unknown. Moreover, the fact that the effects were modest and inconsistent between macrophage lines further calls into question the relevance of the findings. Another concern is that the clinical relevance and reproducibility of the studies is unclear given that the gene expression changes observed when the macrophages were exposed to talc alone or in the presence of E2 have not been compared to publicly available gene expression data from similar studies or ovarian tumors from patients. In addition, if the alterations are influenced by E2, it would be expected that the bulk of the differentially expressed genes would be linked to estrogen signaling. However, the genes at issue have not been previously shown to be responsive to estrogen signaling.⁸⁸

Emi. Some of the same researchers published a follow-up study, Emi et al. (2021).⁹⁰ Rather than validate the biological impact and relevance of the gene expression data reported by Mandarino et al., Emi et al. further investigated the impact of talc and titanium dioxide on the

¹ TalcMDL-Godleski-000118.

epigenome and gene expression using the identical J774 mouse macrophage cell line and high doses of talc (10 ug/well) and E2 (2 ug/mL), which, as discussed above, is not a relevant dose to human physiology. The authors took measurements at only one point in time: 24 hours after exposure. The authors purported to show that both talc and titanium dioxide led to changes in gene expression, which is unsurprising since measurement was taken shortly after substantial cellular insult (i.e., treatment with a megadose of a foreign substance). Once more, these studies do not offer meaningful evidence about the alleged carcinogenicity of talc due to the lack of proper controls, the use of non-physiological doses of E2, the inability to confirm the activation of altered genetic pathways, the failure to specify the consistency of gene expression variations between the two studies, the lack of validation for the dependence of gene effects on estrogen, the use of cell lines rather than primary macrophages, and the lack of in vivo validation or mouse studies to confirm their findings. The authors purport to compare the number of changes in gene expression in talc/estrogen treated cells compared to cells treated with other substances, but that comparison is meaningless, because it is not possible to ascertain the extent to which these supposedly affected genes overlap or the magnitude of any differences in gene expression. Moreover, quantitative real-time PCR is required to validate the microarray data. There is not even a particularly robust discussion of how (or whether) the observed changes would be relevant to immunosurveillance. Merely showing that gene expression within macrophages has been altered, without more, would not indicate that immunosurveillance has been compromised. Moreover, the idea that a single dose of talc would have a profound and global effect on DNA methylation in macrophages is hard to reconcile with the rarity of OC if Emi et al.'s findings were physiologically relevant. That is especially so since the purported changes were observed in just 24 hours. The authors themselves acknowledged that no one else had ever reported DNA methylation in such a short period of time.

Like Mandarino et al.'s findings, Emi et al.'s work is preliminary at best. Once again, the authors acknowledged as much, stating that their study proposed a "hypothesis that merits future testing."

In summary, neither Mandarino et al. nor Emi et al. provides any evidence that cosmetic talc can cause or contribute to malignant transformation in ovarian cancer because neither study used cells that could be (but had not already been) transformed. Moreover, neither study provides any evidence that cosmetic talc can directly affect immunosurveillance in any clinically relevant way because (1) the doses of talc and estradiol used in the studies are of questionable relevance; (2) the cells used in the studies are of questionable relevance; and (3) the results of the studies are unvalidated, modest, and of questionable clinical significance.

Saed/Fletcher/Harper. Dr. Ghassan Saed, whose work is at least partially funded by plaintiffs' lawyers in cosmetic talc litigation, also has not produced any papers that support the conclusion that cosmetic talc induces malignant transformation.

In Fletcher et al. 2019 (an article on which Dr. Saed was the corresponding author), the authors assessed the effects of cosmetic talc on ovarian cancer cells and suggested that it increased ovarian cancer cell proliferation, immune gene expression, and prevented apoptosis.⁷² This manuscript does not even suggest (let alone demonstrate) that cosmetic talc causes malignant transformation. The manuscript also has numerous flaws, including the following:

(1) The cell lines used in the study are not representative of HGSC.

(2) The talc was resuspended in dimethyl sulfoxide (DMSO; Sigma Aldrich) which is known to be toxic to cells when used at high concentrations. Thus, the supposedly observed effects may be due to the high concentration of DMSO.

(3) Decrease in antioxidant enzyme activity observed by ELISA can be attributed to cell death given that the amount of protein lysate across samples is not normalized and DMSO at these high concentrations can induce cell death.

(4) The authors used tetrazolium salt, 3,[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) to measure cell proliferation. However, MTT does not measure proliferation; it measures mitochondrial enzymes. Therefore, the assay described simply looks at cell number at a given timepoint (24 hours), and given that there are no data on how many cells were initially plated in each treatment group, it is difficult to interpret whether there is a difference between the groups.

(5) The investigators claim that talc induces single nucleotide polymorphisms (SNPs), which are mutations that are commonly seen in at least 1% of the population and not commonly pathogenic. These data are difficult to interpret given that there are no data showing chemicals can mutate DNA, especially in such a short period of time; therefore, additional studies are needed to confirm these results. These types of studies have not been documented in the literature before and have not been proven credible; they require proper controls and validation, which was not provided. For example, talc at multiple doses and time points is required to address whether these SNPs are selecting for a certain population of cells with the mutation or whether it is actually causing the mutation. The authors claim that talc can induce SNPs within a 72-hour period, which is not feasible given that acquisition of a genetic mutation – a large number of them, as is claimed in the manuscript – within this short period of time would require selection and passaging of the cells. These experimental defects undermine the validity of the authors' assertion.

Additionally, I was provided with numerous documents pertaining to more recent work performed by Dr. Saed, including several versions of a manuscript drafted by Dr. Saed et al. that

was submitted to and rejected by numerous journals in 2020 and 2021, including Gynecologic Oncology and several other lower-impact journals, including Reproductive Sciences, a publication by the Society for Reproductive Investigation (where Dr. Saed is a member of the Publications Committee). The documents also included an abstract that was accepted as a poster presentation to the Society of Gynecologic Oncology (SGO) 2020 annual meeting. Having been a reviewer for poster abstracts, I know that ~90% of abstracts get accepted to these large annual meetings. The actual acceptance rate for the SGO 2020 meeting, which can be found at [https://www.gynecologiconcology-online.net/article/S0090-8258\(20\)32327-1/fulltext](https://www.gynecologiconcology-online.net/article/S0090-8258(20)32327-1/fulltext), is similar: 842 abstracts were submitted, and 743 (88%) were accepted. The reason why so many abstracts are accepted as a poster presentation is that the reviewers expect that the data presented may be preliminary, and thus they tend to be more lenient in their expectations. Lastly, I reviewed a published manuscript of Dr. Saed's work in a journal called Minerva Obstetrics and Gynecology, which accepted it after multiple rejections from other journals and has an extremely low impact factor of 1.8.⁷⁹ I approached my review of these documents the same way I have reviewed numerous manuscripts, posters and grants for various journals and funding agencies as a peer-reviewer over the past 15 years. As a reviewer, we are blinded to the other reviewers' comments to maintain an unbiased critique of the research study; thus, I began by reading and analyzing all the documents prior to examining the comments from the previous reviewers.

Overall, I had numerous concerns with the data presented, and the conclusions reached by the authors, which are not supported by the experimental evidence. Moreover, the majority of my concerns were consistent with the numerous critiques raised by the peer-reviewers. Interestingly, even one of the co-authors, Dr. Robert Morris, also raised some of my concerns, which were never

addressed by Dr. Saed.² In addition, I was shocked by the lack of transparency, in terms of not always reporting that the source of funding for the studies was from a plaintiffs' law firm. In particular, I was surprised that Wayne State University would allow this type of research collaboration given that Dr. Saed was also serving as an expert witness for talc plaintiffs; this is typically not allowed at most universities. Below, I explain why I believe the data presented do not show that cosmetic talc induces malignant transformation.

1. **Use of incorrect and uncharacterized normal cell lines.** The investigators use primary ovarian epithelial cells purchased from either Cell Biologics or ScienCell Research Laboratories; however, there is no characterization of these lines, and it is not clear whether it was confirmed these cells maintained their epithelial origin. It is stated that these cells were passaged numerous times, but normal cells cannot grow on plastic indefinitely without being immortalized using hTERT or through the loss of various tumor suppressor genes, including p53, RB1, or PTEN. In order to confirm that cosmetic talc is inducing malignant transformation of ovarian or fallopian tube cells, it is essential to start with normal ovarian or fallopian tube cells, and this was not done in these experiments. Second, these studies do not address the transformative potential of cosmetic talc on the most common subtype of ovarian cancer, HGSC, given that FTSEC, which are the precursor cells for this cancer, are not used for these studies.

² SAED_SEPT222021_SUPPL_000151.

2. **Malignant transformation cannot be confirmed using one assay.** To measure cell transformation, the investigators used a single cell transformation assay from Abcam that measures anchorage-independent cell growth over time, which is only one step of transformation (*see* section VI), and this was measured via viable mitochondria using a colorimetric assay. The mitochondria, which is an organelle found in large numbers in most cells, provides the biochemical processes of respiration and energy production for the cell. The investigators found an increase in absorbance signal (which should represent cell number) when cells are pre-exposed to cosmetic talc for 72 hours. There are several concerns with how the assay was performed. First, the investigators did not confirm that equal numbers of cells were plated at the beginning of the experiments as is shown on the manufacturer's website (Figure 3).

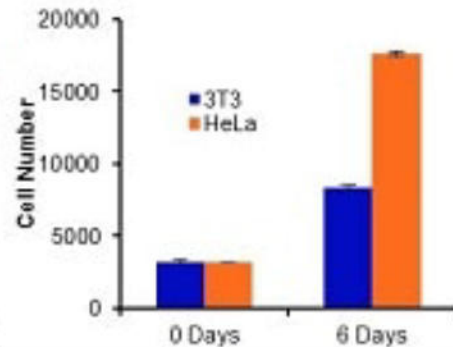


Figure 3: Graph taken from manufacturer's website (<https://www.abcam.com/cell-transformation-assay-kit-colorimetric-ab235698.html#lb>), which shows equal numbers of cells were seeded at the beginning of the study on Day 0 for the Cell Transformation Assay and the cell numbers increased after 6 days.

Second, the blank control did not include talc powder solution to confirm that it does not affect the absorbance. Given that the investigator did not characterize what was in the talcum powder solution after sonication, or whether any of the particles that remain in the solution or in the agar could affect the colorimetric reading, it is important to have a negative control that contains the talc powder solution in order to confirm that it is not altering the absorbance values.

Third, the lack of details on the talc solution is very concerning, especially because talc is insoluble in PBS, and therefore, after the solution is sonicated and filtered, it is not clear what remains in the supernatant. Furthermore, given that the sonicated solution was not analyzed, and talc in the final stock solution was not quantified, it remains unclear how the working concentration

of talc was ascertained. This concern was shared by the peer-reviewers. For example, one reviewer stated that “several critical fatal flaws in the study included no description of talc powder and TiO₂ characteristics.”³ The reviewer also states that “it is surprising that no particle characterization effort was performed” because [m]ost particle-based toxicity studies are now recommended to perform minimal particle characterization.”⁴ In addition, if this dose of talc is accurate, it is very high and most likely not physiological (as discussed above with regard to other studies relied on by plaintiffs’ experts in this litigation). This concern was also raised by the other peer-reviewers. For example, Reviewer 2 for the Gynecologic Oncology submission states, “I also think the dose of talcum powder is extremely high, I calculate it to be 263mM for the lower dose which is unlikely to ever replicate physiological dosing...,”⁵ and interestingly, one of the co-authors of the manuscript, Dr. Morris, sent an email to Dr. Saed asking, “Are the concentrations used physiologically possible (especially in the ovary)?”⁶ To my knowledge, Dr. Saed never replied to this question, and he did not address it in the submitted manuscript.

Fourth, OD values are not correlated with actual number of colony numbers to confirm that the increased cell numbers reflect increased colony numbers. This is especially concerning because the authors do have images of cells; therefore, they could have taken more images and quantified the colonies. This point is crucial given that the assay has not been established by many labs and is not referenced in the literature. This is also important because absorbance can be detecting individual cells that are not in colonies or spheres.

³ SAED_SEPT222021_SUPPL_000101.

⁴ SAED_SEPT222021_SUPPL_000101.

⁵ SAED_SEPT222021_SUPPL_000070.

⁶ SAED_SEPT222021_SUPPL_000151.

Fifth, only one assay that measures transformation is performed, which is not sufficient to determine malignant transformation, as outlined in section VI.

Lastly, there is no analysis of the cells during the 72 hours pre-incubation period with talc. For instance, morphological changes or alterations in proliferation could be observed in these assays; however, nothing was documented (as shown in Figure 2A and B). In sum, transformation is a multi-step process that is measured routinely in the laboratory; however, none of these assays was performed to confirm that cosmetic talc induced malignant transformation. Thus, further data showing transformative changes using more established assays is required to claim that cosmetic talc has transformative abilities. In addition, to state that a single application of a cosmetic talc powder at a very high dose is transformative requires further robust scientific support because given the wide use of this compound one would expect a much higher incidence of cancer, especially ovarian cancer.

Numerous scientists who reviewed this manuscript agreed with my assessment, including Reviewer 1 of PLOS One, who stated: “Soft agar colony formation alone in an in vitro test system is not enough data to claim malignant transformation.”⁷ “To show ‘neoplastic transformation’, authors would need to conduct a more diverse battery of tests to show that these ‘transformed’ cells possess a tumor or cancer cell phenotype ...”⁸ This reviewer also states, “This suggests that a single application of talc is extremely potent and carries high risk for cell transformation. Since talc powder is widely used, why aren’t cancer rates much, much higher? . . . Without adequate discussion or further data to support this claim, this finding is highly questionable.”⁹

⁷ SAED_SEPT222021_SUPPL_000101.

⁸ SAED_SEPT222021_SUPPL_000101.

⁹ SAED_SEPT222021_SUPPL_000101.

3. **Mechanistic insight or molecular changes were not consistent with transformative phenotype.** To confirm that transformation has occurred, the investigators stained the cells with p53 and Ki67 antibodies to assess whether p53 becomes mutated or whether the cells are more proliferative upon cosmetic talc treatment. Unfortunately, neither of these conclusions can be made from these assays, for several reasons. First, it is well known that intense p53 nuclear staining, especially in STIC and ovarian cancer cells, correlates with TP53 missense mutations. Therefore, given that the normal cells have high focal expression of nuclear TP53 may indicate that it already has a TP53 mutation. Thus, in order to confirm TP53 status in these cells, sequencing of the TP53 gene is required, especially given that the large majority of normal ovarian epithelial cells that grow in culture acquire a TP53 mutation.

Second, to accurately assess the expression difference between control and experimental conditions, the immunohistochemistry data need to be quantified and statistical differences between the quantification need to be assessed. Shockingly, there is no quantification of p53 or Ki67 staining on the posters, lab notebooks, or manuscripts submitted to numerous journals.

Third, p53 protein triggers a protective response in the cell and its expression is altered transiently for numerous reasons; thus, it is important to confirm the differences observed over time. In sum, given these deficiencies, no conclusion can be made from the immunohistochemical data, and no molecular changes consistent with ovarian cancer transformation are presented.

Fourth, because most cancers arise from several genetic mutations that accumulate in cells over multiple rounds of cell division, it is not possible that 72 hours of cosmetic talc exposure would be enough time for the numerous mutations needed for malignant transformation to become fixed.

4. **Lab notebook standards not maintained.** I also received pages from Dr. Saed's lab notebook that contained information about the experiments included in the manuscript detailing the role of cosmetic talc and malignant transformation.¹⁰ These documents were also very concerning given that a lab notebook is the legacy of a research laboratory, and it is meant to provide an explanation of why experiments were initiated, how they were performed, and the results of the experiments. Here, the information in the lab notebook lacked details and complete record of procedures. Most notably, the lab notebook should be a record for all the raw data. However, that was clearly lacking in Dr. Saed's lab notebook. Much of the information in the lab notebook more closely resembled a photocopy from the manufacturer's generic protocol than a description of what was actually done in this case, and if one would want to replicate these experiments from the lab notebook, it would be impossible due to the lack of further details, such as those described below. The lack of experimental detail is also reflected in the materials and methods section of the manuscript submitted to several journals. Numerous reviewers noted difficulty in analyzing the data presented given the scarcity of details provided for the assays as well. Below, I provide some examples of what several of the reviewers stated in their critiques of the manuscripts. With almost no exceptions, the lab notebook does not contain additional information that would resolve these criticisms; if anything, it generates more questions and creates more confusion:

- Reviewer #2 for the PLOS One review states: "*The authors fail to tell the reader what density of cells were used for these experiments. 24 wells? 96 wells? All relevant information is missing.*"¹¹

¹⁰ SAED_SEPT222021_SUPPL_000161-171.

¹¹ SAED_SEPT222021_SUPPL_000103.

- Reviewer 1, Gyn Onc: *“Several phrases describing cell culture and colorimetric assay within the methods and discussion appear to be taken verbatim from the manufacturers’ websites ...”*¹²
- Reviewer 2, Gyn Onc: *“Ultimately these data are too premature for publication, the authors present very preliminary in vitro data suggesting that talcum powder may induce malignant change in normal ovarian epithelial cells, but not in fibroblasts. The data are premature, restricted to two cell lines and really offer no significant mechanistic insight.”*¹³
- Editor, PLOS One: *“Both reviewers have raised serious concerns about the experimental design, analyses and interpretation of the findings.”*¹⁴
- Reviewer 1, PLOS One: *“Based on the minimal amount of data provided in this manuscript, the authors’ conclusions suggesting acute exposure of talc powder to ovary epithelial cells is associated with ovarian cancer are outrageous and not supported by the manuscript’s data.”*¹⁵
- Reviewer 1, PLOS One: *“The method for particle exposure to ovarian cells is not adequate. What was the seeding density in each well and what size wells were used? What size were the talc powder particles and TiO₂ particles in cell culture medium during exposure? How were exposed cells handled and transferred to the colony*

¹² SAED_SEPT222021_SUPPL_000070.

¹³ SAED_SEPT222021_SUPPL_000070.

¹⁴ SAED_SEPT222021_SUPPL_000100.

¹⁵ SAED_SEPT222021_SUPPL_000101.

formation assay? ... Page 5 states that the negative control was a blank. If so, how can you have a positive percent transformed cell response for this treatment?”¹⁶

- When commenting on the materials and methods section, reviewer 2 of the PLOS One submission states, “*The lack of detail in this section makes this paper extremely difficult to follow.*”¹⁷
- When commenting on a subsection of the materials and methods section, reviewer 2 of the PLOS One submission states, “*I have no idea what I am reading here. First the authors talk about an agarose assay, then WST, and now they are combined? This is very poorly explained.*”¹⁸
- Again, reviewer 2 of the PLOS One submission states with clear frustration, “*The authors mention malignant transformations observed in cells, but where was the methodology for this? I did not see any carcinogenic assays[.] I did not see any methodology for detecting malignant transformations.*”¹⁹
- Lastly, given the lack of experimental details, it was difficult to interpret a lot of the data, and this was also articulated by the majority of the reviewers. Reviewer 2 of the PLOS One submission states, “*If the authors do not tell the reader which one of their methods was used to detect cell malignancies, then how is the reader supposed to just understand this results section?*”²⁰

¹⁶ SAED_SEPT222021_SUPPL_000102.

¹⁷ SAED_SEPT222021_SUPPL_000103.

¹⁸ SAED_SEPT222021_SUPPL_000103.

¹⁹ SAED_SEPT222021_SUPPL_000103.

²⁰ SAED_SEPT222021_SUPPL_000103.

5. **Conflicting Data.** Another concerning aspect of Dr. Saed and his team's studies was the unreliable and inconsistent nature of how the data were presented in the various posters and manuscripts. For example, the poster abstract submitted to the SGO, which ultimately grew into the 2023 publication, stated that "no colonies formed in normal fibroblasts treated with talcum powder," and "[t]here were no detectible transformed cells when treated with TiO_2 ." However, this is incorrect based on the data in their lab notebook, where colonies in the fibroblasts or the quantification and absorbance values from the fibroblast experiments are missing. Furthermore, the data presented in their own figures in the excel files, lab notebook, manuscripts and posters reveal that all conditions have colonies, including the TiO_2 treated cells; however, it is consistently noted in all posters and manuscripts that the control cells do not form colonies. Thus, it is very confusing how they could state that there were no colonies detectable in these conditions.

In addition, there is a discrepancy in the interpretation of the Ki67 quantification from the immunohistochemistry experiments. For instance, in the lab notebook, the staining in the HOSEPIC-control cells states that Ki67 staining is 70% and the -talc treated is 50%;²¹ however, the poster and manuscripts report that an increase in the proliferation index (Ki67) was observed in talcum powder-treated versus controls. Even more confusing, the lab notebook states that HOSEPIC-control cells have mutated p53 and HOSEPIC-talc treated cells were wild-type p53, but the posters and manuscripts report the opposite.²² Another discrepancy between that SRI poster in 2021 and the lab notebook is that the poster states that the researchers ran a TiO_2 control on the p53/Ki67 staining, but the lab notebook does not indicate this and no images from these cells are shown.²³ Moreover, the statistical methods used to assess the relevance of the IHC staining is

²¹ SAED_SEPT222021_SUPPL_000171.

²² SAED_SEPT222021_SUPPL_000171.

²³ SAED_SEPT222021_SUPPL_000169-171.

unclear and never shown. As stated by Reviewer 1 from the Gynecology Oncology submission:
*“The authors conclude that proliferative index is elevated to 90%, but do not show evidence or statistical analysis to this effect. Moreover, the methods describe a binary method of scoring Ki-67 of high or low, calling into question how the 90% value was generated.”*²⁴

In sum, the discrepancies I observed between the posters, manuscripts and lab notebook make me question all the results presented by Dr. Saed and I could not trust the data. I agree with the majority of the peer-reviewers who reviewed the manuscript, especially Reviewer #2 for PLOS One, who stated *“The problems with this submission are too numerous to count, and the science, methodology, and data cannot be trusted.”*²⁵

Dr. Saed also recently published a review article, in which he repeats his claim to have “unequivocal evidence” that talc “induces molecular changes that mimic the hallmarks of cancer,” but also acknowledges that “[t]he mechanism by which talc might contribute to an increased risk of developing ovarian cancer is not entirely clear.”¹⁰³ The article mostly repeats the findings from the papers his group has previously published, and therefore cannot be trusted for all the reasons just discussed. To the extent it mentions other literature, it selectively highlights certain results. For instance, the article notes certain changes in gene expression observed in Shukla, et al. (2009) but fails to acknowledge those authors’ conclusion that “nonfibrous talc is regarded as noncarcinogenic” and cells “adapt to or undergo repair after exposure to this mineral.”¹⁰⁴

O’Brien. A few weeks ago, a new paper, O’Brien 2024, combined prospective and retrospective data from the Sister Study, along with “imputations” and “corrections,” to derive various risk ratios assessing a potential association between (among other things) genital talc use

²⁴ SAED_SEPT222021_SUPPL_000070.

²⁵ SAED_SEPT222021_SUPPL_000104.

and ovarian cancer.¹⁰⁵ I understand that other experts are addressing the main findings of the paper. I just briefly note that the authors acknowledge that their results “*do not pinpoint a specific cause or mechanism*” and condition their policy recommendations on whether “*the underlying biologic mechanisms and causal agents can be confirmed.*” Moreover, according to the authors themselves, “*These results do not establish causality and do not implicate any specific cancer-inducing agent. Those reporting talc use could be recalling products that contained talc, cornstarch, or a mixture, and women may have used different products at different times.*” This paper does not alter my opinion that identification of the precise chemical agent and functional validation of this agent’s effect on the transformation of normal cells via the assays outlined in Section IX would be necessary to establish causality.

I hold all the opinions expressed in this report to a reasonable degree of scientific certainty.

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EXHIBIT A

Analisa DiFeo, Ph.D.
Professor, Department of Pathology
Professor, Department of Obstetrics & Gynecology
Associate Director, Cancer Biology Graduate Program
University of Michigan, Michigan Medicine
1600 Huron Parkway, Ann Arbor, Michigan 48109 Office:
(734) 936-5685, Cell: (516) 528-5126
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Education and Training

Education

09/1997-05/2001	BS, State University of New York at Binghamton Binghamton, NY
06/2004-03/2008	PhD, Icahn School of Medicine at Mount Sinai, New York, NY

Postdoctoral Training

03/2008-07/2012	Postdoctoral Fellow, Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, NY
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Work Experience

Academic Appointment

03/2012-06/2018	Assistant Professor, Division of General Medical Sciences (Oncology), Department of Medicine, Case Western Reserve University School of Medicine, Cleveland
07/2014-06/2018	Assistant Professor, Department of Genetics and Genome Sciences, Case Western Reserve University School of Medicine, Cleveland
10/2014-06/2018	Norma C. and Albert I. Geller Designated Professor in Ovarian Cancer Research, Case Western Reserve University School of Medicine, Cleveland
01/2016-01/2018	Director, Xenograft and Preclinical Therapeutics Core, Case Western Cancer Center, Cleveland, Ohio
07/2018-05/2024	Associate Professor, University of Michigan, Department of Pathology, Department of Obstetrics and Gynecology, Ann Arbor (Tenured)
01/2021-Present	Co-Director, Cancer Biology Training Program, University of Michigan, Ann Arbor, Michigan
01/2023-Present	Associate Director, Cancer Biology PhD Program, University of Michigan, Ann Arbor, Michigan
05/2024-present	Professor, University of Michigan, Department of Pathology, Department of Obstetrics and Gynecology, Ann Arbor (Tenured)

Administrative Appointment

01/2011-Present	Co-Founder, Chair of Scientific Advisory Board, The Young Scientist Foundation, Ann Arbor, MI
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Analisa DiFeo, PhD

01/2012-01/2018	Founder and Director, Gynecologic Oncology Translational Research Group, Cleveland, Ohio
01/2013-01/2018	Elected Member, Faculty By-laws Committee, Case Western Reserve University, Cleveland, Ohio
01/2016-01/2018	Elected Vice Chair, Committee on Biomedical Research, Research Infrastructure Council, Case Western University, Case Western Reserve University
01/2018-Present	Member, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan
01/2019-Present	Diversity Ambassador, Program in Biomedical Sciences (BIPS) program, University of Michigan, Ann Arbor, Michigan
01/2019-01/2022	Senate Assembly, University of Michigan, Ann Arbor, Michigan
01/2020-Present	Member, Medical Affairs Advisory Committee (MAAC), University of Michigan, Ann Arbor, Michigan
01/2020-01/2022	Editorial Board Member, Endocrinology, Oxford Academic Journals, Oxford, United Kingdom
03/2021-Present	Expert Witness, Faegre Drinker Biddle & Reath LLP, Johnson & Johnson Consulting, Florham Park, New Jersey 07932
01/2022-Present	Co-Chair, Mission Boost Grant Peer Review Committee, American Cancer Society, Kennesaw, Georgia
01/2022-Present	Member, Animal Care and Use Faculty Advisory Committee, University of Michigan, Ann Arbor, Michigan
01/2022-Present	Director, Michigan Ovarian Cancer Science, and Innovation Consortium (MOSAIC), University of Michigan, Ann Arbor, Michigan
01/2022-Present	Chair, Medical Affairs Advisory Committee (MAAC), University of Michigan, Ann Arbor, Michigan
01/2023-Present	Board Member, Michigan Ovarian Cancer Alliance (MIOCA), Ann Arbor, Michigan
08/2023-Present	Associate Editor, Frontiers in Oncology (Gynecological Oncology), Lausanne, Switzerland
09/2023-Present	Member, Rackham Predoctoral Committee for Biological and Health Sciences, University of Michigan, Ann Arbor, Michigan

Research Interests

- Functional characterization of pathways driving of ovarian cancer
- Development novel therapeutic approaches to enhance ovarian cancer patient survival.
- Identification of novel biomarkers and drivers for early detection or therapeutic response
- Generation of patient-relevant mouse models

Grants

ACTIVE

Title: B55 alpha deficiency as a therapeutic target in cancer

Time Commitments: 1.08 calendar

Funding Agency: Ohio State University/ NIH - R01 CA240374 (PI: Zhang)

Performance Period: 07/01/2020 – 06/30/2025

Level of Funding: \$58,340.00

Analisa DiFeo, PhD

Goals/Aims: Evaluating the efficacy of ATR and CHK1 inhibitor in targeting B55a-defective ovarian cancer.

Role: Co-Investigator

Overlap: There is no scientific, funding or effort overlap.

Title: Ovarian cancer projects

Time Commitments: 0.01 Calendar Months

Funding Agency: University of Michigan

Performance Period: 10/29/2018 – 10/28/2028

Level of Funding: \$7,500

Goals: Use of Tumor Repository and PDX bank in order to uncover biomarkers for drug response

Specific Aims: N/A

Role: Principal Investigator

Overlap: There is no scientific, funding or effort overlap.

Title: Cancer Biology Training Program

Time Commitments: 0.6 calendar

Funding Agency: NIH/NCI (T32CA009676)

Performance Period: 9/30/1997-8/31/2024 (NCE)

Level of Funding: \$1,388,990

Goals: This award supports graduate and post-graduate training in Cancer Biology at the University of Michigan. Dr. DiFeo's effort for this award is support mainly by cost-share with the Rogel Cancer Center and the Medical School.

Specific Aims: NA

Role: Multiple PI

No scientific or budgetary overlap.

Title: Treatment of Homologous Recombination Proficient Ovarian Cancer and PARP Inhibitor-Resistant Tumors Using PP2A Re-Activation Strategies

Time Commitments: 1.8 Calendar Months

Funding Agency: Department of Defense (OC210149)

Performance Period: 5/1/2022 – 4/30/2025

Level of Funding: \$702,000

Goals: Assess whether Small Molecule Activators of PP2A (SMAPs) can confer a "BRCAness" phenotype in HGSOC tumors to sensitizes tumors to DNA repair inhibitors such as PARPi, thus allowing for expanding the patient population that can benefit from PARPi therapies

Role: PD/PI

Overlap: There is no scientific, funding or effort overlap.

Title: Examining the role of the miR-181a:Wnt/B-catenin axis in ovarian cancer

Time Commitments: 2.64 Calendar Months

Funding Agency: NIH/NCI (R01CA197780)

Performance Period: 4/6/2023 – 3/31/2028

Level of Funding: \$1,906,182

Goals: The overall goal of this study is to develop an effective STING reactivation strategy by inhibiting miR-181a to activate a powerful anti-tumor immune response which can then be combined with complimentary existing therapies to prevent HGSOC progression and recurrence.

Role: PD/PI

No scientific or budgetary overlap.

Analisa DiFeo, PhD

Title: Profiling the Fluid Assisted Dissemination of Pre-malignant cells in Fallopian Tubes

Time Commitments: 0.6 Calendar Months

Funding Agency: NIH

Performance Period: 7/7/2023 – 6/30/2028

Level of Funding: \$2,468,0178

Goals/Aims: Aim 1: Characterize dissemination of the FTSEC due to shear stress in the in vitro microfluidic models. Aim 2 Research Approach: A2.1: Analyze the gene expression changes of shear stress stimulated FTSEC. Aim 3: Determine if shear stress stimulated FTSEC are capable of tumor initiation in vivo.

Role: Co-I

No scientific or budgetary overlap.

Title: Determine the efficacy of Muc-1-ADC in patient relevant ovarian cancer models

Time Commitments: 1.8 Calendar Months

Funding Agency: SPARC/SUN PHARMA

Performance Period: 3/31/2023 - 3/30/2025

Level of Funding: \$534,060

Goals: The overall scope of this proposal is to utilize the robust pre-clinical tumor models that have been developed in the laboratory, to examine the clinical efficacy of Muc-1-ADC to confirm that advanced stage chemotherapy resistant ovarian cancer is the optimal tumor subtypes for clinical development and assess whether miR-181a may be an appropriate biomarker for use in early phase clinical trials.

Role: PD/PI

No scientific or budgetary overlap.

Title: Determining a role for PP2A in the development and treatment of endometriosis

Time Commitments: 0.24 calendar months

Funding Agency: DoD

Performance Period: 1/15/2023 – 1/14/2025

Level of Funding: \$312,000

Goals: To determine if mutations to PP2A are a molecular driver of endometriosis development, and if small molecule modulation of PP2A is a viable treatment option.

Role: Co-I

No scientific or budgetary overlap.

Title: Therapeutic Modulation of the Serine/Threonine Phosphatase PP2A for the Treatment of Uterine Serous Cancer (USC) and Uterine Carcinosarcoma (UCS)

Time Commitments: 1.2 Calendar Months

Funding Agency: DoD

Performance Period: 9/1/2024 – 8/31/2027

Level of Funding: \$1,555,176

Goals: Discover new therapies for the treatment of high grade uterine cancers

Specific Aims: AIM 1: Define the therapeutic efficacy of the lead PMG in a series of high-grade uterine cancer xenograft and PDX models. AIM 2: Elucidate the functional relevance and mechanistic basis of A-B56a-C stabilization in uterine cancer cells and xenografts. AIM 3: Explore combinations therapies with PMGs using in vivo xenograft models of uterine cancer.

Contact: TBD

Role: Co-I

Analisa DiFeo, PhD

No scientific or budgetary overlap.

Title: Ultrasensitive detection of circulating PRAME as a 'binary' blood biomarker for endometrial cancer

Time Commitments: 0.4 calendar

Role: Co-I

Funding Agency: Department of Defense

Performance Period: 02/01/2024 – 01/31/2026

Level of Funding: \$587,862

Project Goal: The proposed work addresses the PRCRP Topic Area of endometrial cancer (EC) and the PRCRP Overarching Challenge in developing minimally invasive methods for cancer detection and recurrence prediction. We will address gaps in early detection of EC that can impact mission readiness and the health of military members and their families, by developing an ultrasensitive blood test for the early, accurate detection of EC, particularly aggressive, high-risk cases.

Overlap: None

PENDING

Title: Cancer Biology Training Program

Time Commitments: 0.6 calendar

Funding Agency: NIH/NCI (T32CA009676) (Renewal)

Performance Period: 9/01/2024-8/31/2029

Level of Funding: \$2,446,760

Goals: To train exceptional junior investigators to address fundamental biological problems related to human cancer.

Role: Multiple PI

No scientific or budgetary overlap.

Title: Bridging Immune Response and Nanotechnology through the targeting of miR181a

Time Commitments: 1.2 calendar months

Funding Agency: NCI/NIH

Performance Period: 9/1/2024 – 8/31/2029

Level of Funding: \$1,274,158

Goals: The laboratory of Dr. DiFeo will be responsible for performing the studies proposed in specific aim 2, as well as providing the mir-181a antigomers for the preparation of nanoparticles. Her research staff will (1) coordinate with Dr. Lopez-Bernstein's group to receive the nanoparticles; (2) establish the in vivo models; (3) test miR-181a targeting drug, STING agonist and immunotherapies in vivo followed by flow cytometry and IHC/IF to determine immune cell activation; (4) discuss and plan work for these studies with the Lopez- Bernstein lab and other co-investigators, and agree to share all data.

Contact: TBD

Role: PD/PI

No scientific or budgetary overlap.

PREVIOUS

Title: Validating AI predicted targets in a clinically relevant patient derived cisplatin resistant ovarian cancer 3D model

Benevolent AI Collaboration (DiFeo, PI) 10/01/2018 – 06/30/2022 (NCE) 1.08 Calendar Months

Benevolent AI \$48,360

Goals: We aim to validate predictions generated in silico using AI and machine learning to target CSC and cisplatin resistant mechanisms in recurrent resistant ovarian cancer.

Role: Principal Investigator

Analisa DiFeo, PhD

Overlap: There is no scientific, funding or effort overlap.

Title: Examining the role of the miR-181a:Wnt/B-catenin axis in ovarian cancer recurrence

R01CA197780 (PI: DiFeo) 4/1/2016-12/31/2021 3.60 calendar

NIH/NCI \$238,870

Goals: We aim to test the hypothesis that miR-181a activation of the Wnt signaling pathway plays a hitherto unappreciated role in the emergence of HGSOc platinum-resistance through the maintenance of CICs thus introducing a novel targetable pathway for the treatment of chemoresistant HGSOc. In order to substantiate this hypothesis we will establish the mechanism by which miR-181a regulates the Wnt signaling pathway, functionally assess Wnt-driven tumor cells isolated from primary HGSOc tumors and lastly, investigate the therapeutic benefits of selectively targeting the Wnt signaling pathway.

Role: Principal Investigator

Title: Treatment of Ovarian Cancer: Aim # 2

Shaughnessy Family Foundation (PI: DiFeo) 8/01/2018 – 12/31/2021 (NCE) 1.08 Calendar Months

Sponsor: Shaughnessy Family Foundation \$99,022

TO Case Western Reserve Univ

Goals: Upon completion of this aim, faculty will have established pharmacodynamics in multiple mouse

models, with data from patient-derived mouse models of greatest importance. These findings will demonstrate the pre-clinical efficacy of VLP and inspire funding from external sources {i.e. pharma, Harrington Institute, NIH, foundations) to advance toward drug development and eventual clinical trials.

Role: Principal Investigator

Overlap: There is no scientific, funding or effort overlap.

Title: Targeting miR-181a-STING Signaling for the Treatment of Ovarian Cancer

Rogel Cancer Center Research Grant 12/1/2019-11/30/2021 1.08 Calendar Months

Sponsor: University of Michigan Source Country: USA

Annual Direct Costs: \$75,000 Total Award Amount: \$75,000

Role: Principal Investigator

Title: SMAPs for the Treatment of Ovarian Cancer

W81XWH-16-1-0587 (DiFeo, PI) 09/01/2016-3/30/2021 (NCE) 3.00 calendar

Sponsor: Department of Defense \$147,812

Goals: Determine the effects of Small Molecule Activators of PP2A (SMAPs) on clinically relevant PDX models of ovarian cancer, assess the mechanism of SMAP-induced degradation of PLK1 and its associations with anti-tumor activity in vivo, and exploit SMAPs effects on PLK1 and the DNA damage response pathways to sensitize ovarian tumors to other DNA damage targeting drugs.

Role: Principal Investigator

Title: PTP μ as a targeting agent for ultrasound-enhanced treatment of ovarian cancer

Mary Kay Ash Charitable Foundation (PI: Brady-Kalnay) 07/01/2017 – 06/30/2019 0 calendar

The Mary Kay Foundation \$43,478

Goals: To develop an Ovarian Cancer image-guided drug delivery system composed of a novel OC-targeting agent directed towards tumor-specific fragments of PTP μ .

Role: Co-PI

Title: OutRun Ovarian Cancer (OROC) (PI: DiFeo) 01/15/2018– 07/01/2019 0.6 calendar
 Philanthropic Funds \$50,000.00
 Use of Tumor Repository and PDX bank in order to uncover biomarkers for drug response
 Role: Principal Investigator
 Michigan Drug Discovery 07/01/2019-6/30/2021 1.08 Calendar Months
 Sponsor University of Michigan Source Country: USA
 Annual Direct Costs: \$7,500 Total Award Amount: \$7,500
 Development of miR-181a inhibitors for the treatment of cancer
 Role: Principal Investigator

Title: Testing of Small Molecule PP2A Activators in Gynecological Cancer
 Time Commitments: 0.6 Calendar Months
 Funding Agency: Rappta Therapeutics Oy
 Performance Period: 9/1/2020 - 12/31/2022
 Level of Funding: \$172,067.85
 Goals: This budget represents the testing of EV440 and EV612 in genetically distinct patient-derived cell lines: endometrial cancer, high grade serous ovarian cancer (HGSOC), isogenic platinum-resistant HGSOC, isogenic PARPi resistant HGSOC and non-transformed fallopian tube.
 Role: Co-Investigator
 Overlap: There is no scientific, funding or effort overlap.

Title: Identification of Chemical Entities that Regulate OncomiR-181a
 Time Commitments: 0.01 Calendar Months
 Funding Agency: Michigan Drug Discovery (MDD Screening Award)
 Performance Period: 7/1/2021-1/31/2023
 Level of Funding: \$70,000
 Goals: High-throughput drug screen using miRNA-181a biosensor to identify miR-181a targeting drugs.
 Role: PD/PI
 Overlap: There is no scientific, funding or effort overlap.

Patents / Disclosures

Development of primary endometrial and ovarian cancer cell lines and patient-derived xenograft models, Hera BioLabs License Agreement, A2017-11084, 01/17/2017

Compositions and methods for treating cancer, Author, US, 4/1/2016.

Biomarker Associated with Risk of Melanoma Recurrence, US 2015/0218649 A1, Author, US, 8/1/2012.

Honors and Awards

National

2009	AACR AstraZeneca Scholar-in-Training Award, AACR Annual Meeting, United States
2014	Liz Tilberis Scholar Award, Ovarian Cancer Research Fund, New York, NY, United States
2014	Norma C. and Albert I. Geller Designated Professor in Ovarian Cancer, Case Western University School of Medicine

2016	The Nsoroma Science Award, National Technical Association, Cleveland Chapter
2016	Invited Spark Speaker, Annual Conference of Healthcare Businesswoman's Association, United States
2022, 2023	ResearchHER American Cancer Society Ambassador, American Cancer Society, Kennesaw, Georgia
2023	Association of American Cancer Institutes (AACI) and American Association for Cancer Research (AACR) annual Hill Day Participant, Washington, DC,

Regional

2014	Crain's Forty Under 40, Crain's Cleveland Business, Cleveland, OH, United States
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Institutional

2005	Travel Award, Mount Sinai School of Medicine, Graduate School, United States
2007	Travel Award, Mount Sinai School of Medicine, Graduate School, United States
2008	Terry Krulwich Doctoral Dissertation Award, Mount Sinai School of Medicine, United States

Study Sections, Editorial Boards, Journal & Abstract Review

Study Sections

International

2012 - present	Grant Peer Reviewer, Molecular Research Council (MRC) Molecular and Cellular Medicine Board, One Kemble Street, London WC2B 4AN
2012	Portuguese Foundation for Science and Technology (Grant Peer Reviewer)
2014	The Wellcome Trust DBT Indian Alliance (Grant Peer Reviewer), The Wellcome Trust DBT Indian Alliance (Grant Peer Reviewer)
2017 - present	Agence Nationale de la Recherche (ANR), RHU-S Hospital and Academics Research in Health Area, French NIH study section (Grant Peer Reviewer)
2018 - present	Grant Reviewer, Cancer Research UK, Research Committee, United Kingdom, (Standing Member)
2019 - present	Grant Reviewer, University "Forco Italio" of Rome, Italy Research Council, Italy, (Standing Member)
2022 - present	Grant Reviewer, KU Leuven Research Council, University of Leuven, Belgium, (Standing Member)
2022- present	Grant Reviewer, The French Ministry of Health, and the National Cancer Institute of France (INCa), Boulogne-Billancourt, France (Grant Peer Reviewer)

National

2009 - 2011	Peer Reviewed Medical Research Program (PRMRP) Osteoporosis and related bone disease Peer Review Panels, United States Department of Defense,
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2012 - 2013	Department of Defense. Peer Reviewed Medical Research Program (PRMRP) Neuroblastoma Peer Review Panels,
2014 - present	Department of Defense, Peer Reviewed Medical Research Program (PRMRP) Ovarian Cancer Peer Review Panels
2014	The Mary Kay Foundation Research Review Committee,
2014	Collaborative Funding Grant (CFG) program, North Carolina Biotechnology Center,
2016 - 2018	Career Enhancement Program (CEP) and/or Developmental Research Program (DRP), Roswell-UPMC Ovarian Cancer SPORE,
2017 - 2018	NIH/NCI Developmental Therapeutic Study Section (R01, R21),
2017	NIH/NCI PDX Network (U54/U24): RFA-CA- 17-003 and RFA-CA- 17-004, (AdHoc)
2018	Michigan Ovarian Cancer Alliance (MIOCA), Ann Arbor, MI,
2018 - present	Breast Cancer Peer Review Panels, Department of Defense, Peer Reviewed Medical Research Program (PRMRP), (Standing Member)
2019 - present	Charter Member, NIH/NCI Developmental Therapeutics Study Section, (Standing Member)
2020 - present	Charter Member, Mission Boost Grant Peer Review Committee, American Cancer Society, (Standing Member)
2020 - present	Charter Member, Team Science Award, Medical College of Wisconsin Cancer Center, Cancer Center Pilot Grant Program Review Committee, (Standing Member)

Regional

2013 - present	Protocol Review and Monitoring Committee (PRMC), University Hospital Cleveland Medical Center, Cleveland, OH (Permanent Reviewer)
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Institutional

2016	American Cancer Society-Pilot Awards, Case Western Reserve University, Cleveland, OH,
2016	CTSC Annual Pilot Review Committee, Case Western Reserve University, Cleveland, OH,
2017	Internal Advisory Board, Adolescent Young Adult Group, Case Comprehensive Cancer Center, Cleveland, OH (Standing member)
2020-present	Biomedical Research Council (BMRC) Member, The University of Michigan, Ann Arbor, MI (Standing member)
2021-present	Rogel Cancer Center Research Committee (CRC) member, The University of Michigan, Ann Arbor, MI (Standing member)

Editorial Boards / Journal & Abstract Reviews

Journal Review (Ad hoc)

2012 - present	Molecular Cancer Research
2012 - present	Science
2012 - present	Scientific Reports
2012 - present	Nature Reports

2012 - present	Molecular Cell
2012 - present	Cell Reports
2012 - present	Cancer Cell
2012 - present	PLoS ONE
2012 - present	BMC Cancer
2012 - present	Journal of Molecular Endocrinology 2012
- present	Cancer Biomarkers
2012 - present	British Journal of Cancer
2012 - present	American Journal of Pathology 2012
- present	Journal of Ovarian Research
2012 - present	Gynecologic Oncology
2012 - present	Endocrinology (Editorial Board member 2020-22)
2012 - present	Oncogene
2012 - present	Oncotarget
2012 - present	EMBO Biology
2012 - present	Molecular Cancer Therapeutics 2012
- present	Molecular Cancer
2014 - present	Cancer Research
2018 - present	Analytical Cellular Pathology
2018 - present	JCO Precision Oncology
2019 - present	American Journal of Pathology
2019 - present	Free Radical Biology and Medicine
2020 - present	Cell Death and Disease
2020 - present	Nature Communications
2021 - present	Human Molecular Genetics
2021 - present	eLife
2021 - present	Journal of Clinical Investigation
2021 - present	Science Reports
2022- present	Nuclear Medicine
2022 - present	BMC Cancer

Teaching

Mentorship

Junior Faculty

2023- present
Analisa DiFeo, PhD

Zhen Ni Zhou, University of Michigan Health,

Ann Arbor, MI, Division of Gynecology Oncology
Currently, Clinical Assistant Professor, University
of Michigan Health, Ann Arbor, MI, Division of
Gynecology Oncology

Clinical Fellow

2011-2012 William H. Bradley, Mount Sinai Medical Center,
New York, NY, Division of Gynecology Oncology,
Currently, Professor, Froedtert Hospital and
Medical College of Wisconsin

2011-2012 Valentin Kolev, Mount Sinai Medical Center, New
York, NY, Division of Gynecology Oncology,
Currently Professor, Mount Sinai Medical Center,
New York, NY

2013-2014 Sareena Singh, University Hospitals of
Cleveland, Cleveland, OH, Division of
Gynecology Oncology, Currently Clinical
Assistant Professor of Obstetrics and
Gynecology, Northeast Ohio Medical University

2014-2015 Amy Armstrong, MD, University Hospitals of
Cleveland, Cleveland, OH, Division of
Gynecology, Currently, Residency Program
Director, Obstetrics and Gynecology, UH
Cleveland Medical Center

2015-2016 Randi S. Connor, MD, University Hospitals of
Cleveland, Cleveland, OH, Division of
Gynecology Oncology, Currently, an attending
physician in Gynecology Oncology at Erlanger
Health System, Chattanooga, TN

2015-2017 Gretchen Garbe, MD, University Hospitals of
Cleveland, Cleveland, OH, Division of
Gynecology Oncology, Currently, an attending

Analisa DiFeo, PhD

physician at Prestige Medical Group, Santa Ana,
CA

2016-2017 Elizabeth Hopp, MD, University Hospitals of
Cleveland, Cleveland, OH, Division of
Gynecology Oncology, Currently, Assistant
Professor Froedtert Hospital and Medical
College of Wisconsin

2017-2018 Christa Dominick, MD, University Hospitals of
Cleveland, Cleveland, OH, Division of
Gynecology Oncology, Currently, Physician at
Sutter Medical Group, Sacramento, CA

Postdoctoral Fellow

01/2013-01/201 Anil Belur Nagaraj, Case Western Reserve University, Cleveland, OH,
Department of Medicine, Currently, Director of Medical and Scientific Affairs at
Vereo Communications, LLC

04/2019-04/2020 Matthew Knarr, PhD, University of Michigan, Ann Arbor, MI, Department of
Pathology, Currently, post-doctoral fellow at University of Pennsylvania,
Philadelphia, PA

03/2019-present Sreeja Sekhar, PhD, University of Michigan, Ann Arbor, MI, Department of
Pathology

04/2021-present Jose Colina, PhD, University of Michigan, Ann Arbor, MI, Department of
Pathology

Medical Student

01/2013-01/2014 Aditya Parikh, MD with research distinction awarded 2014, Case Western
Reserve University, Currently, an attending physician at University of
Pennsylvania, Philadelphia, PA

01/2013-01/2014 Danielle Peress, MD with research distinction awarded 2014, Case
Western Reserve University,

01/2015-07/2018 Olga Kovalenko, MD recipient of Brian Werbel Memorial Fund, Case
Western Reserve University, Currently, Chief Resident, Division of
Gynecology Oncology, University Hospitals of Cleveland, OH

Analisa DiFeo, PhD

01/2016-07/2018 Arshia Surti, MD recipient of Brian Werbel Memorial Fund, Case Western Reserve University, Currently, Resident IV / PGY4, UCLA Health, Los Angeles, CA

Graduate Student

01/2014-01/2015 Heather Cottage, Case Western Reserve University, master's Thesis Advisor, Currently, Physician Assistant at Butler Health System, Butler, PA

01/2015-01/2016 Alexandria Milan, Case Western Reserve University, master's Thesis Advisor, Currently, Physician Assistant at Cleveland Clinic Foundation, Cleveland, OH

01/2015-01/2017 Sandra Mantilla, Case Western Reserve University, master's Thesis Advisor, Currently, Quality Engineer II, Boeing, Everett, Washington

01/2016-04/2018 Erin Ponting, Case Western Reserve University, PhD Thesis Mentor, Currently, Consultant at Newry Corp, Cleveland, OH

01/2014-03/2020 Matthew Knarr, Case Western Reserve University, PhD Thesis Mentor, Currently, post-doctoral fellow at University of Pennsylvania, Philadelphia, PA

01/2017-04/2023 Rita Avelar, University of Michigan, PhD Thesis Mentor, Currently, post-doctoral fellow at University of Michigan, Ann Arbor, MI

01/2019-present Jessica McAnulty, Molecular Cellular Pathology, The University of Michigan, PhD Thesis Mentor, Advancing toward degree.

2019 Kristian Lossel, Cancer Biology rotation student, The University of Michigan, Ann Arbor, MI, Advancing toward degree.

2019 Daniela Gomez Zubieta, MSTP rotation student, The University of Michigan, Ann Arbor, MI, Advancing toward degree.

2020 Kassidy Jungles, PIBS rotation student, The University of Michigan, Ann Arbor, MI, Advancing toward degree.

01/2020-present Noah Puleo, Molecular Cellular Pathology, PhD Thesis Mentor, The University of Michigan, Advancing toward degree.

04/2022-present Grace McIntrye, Molecular Cellular Pathology, PhD Thesis Mentor, The University of Michigan, Advancing toward degree.

2022 Nicole Dean, Cancer Biology rotation student, The University of Michigan, Advancing toward degree.

2022 Julia Ugras, Cancer Biology rotation student, The University of Michigan, Advancing toward degree.

2022 Franchesca Fonseca-Lanza, Cancer Biology rotation student, The University of Michigan, Advancing toward degree.

Undergraduate Student

01/2014-01/2016 Tiffany Seik-Ismail, Case Western Reserve University, Currently, Medical student, Western University of Health Sciences, Pomona, California,

01/2016-01/2017 Alexis Fleming, The Ohio State University, Medical student at University of Cincinnati, Cincinnati, OH

01/2017-01/2018 Patrick Balsom, Case Western Reserve University, Working on Graduate degree.

01/2019-01/2020 Emma Gijbbers, University of Michigan, Working on advanced degree.

01/2019-01/2022 Riya Gupta, University of Michigan, Publication, Continuing to medical school.

01/2019-01/2022 Grace Carvette, University of Michigan, Publication, Continuing to medical school.

01/2019-01/2022 Alexander Sobek, University of Michigan, Research Technician, University of Michigan, Ann Arbor, MI

01/2020-01/2022 Agharan Singh, University of Michigan, Curriculum Mentorship

01/2021-Present Margaret Farah, University of Michigan, Curriculum Mentorship

01/2022-Present Paula De Benedetto, University of Michigan, Curriculum Mentorship

01/2022-Present Amber Farah, University of Michigan, Curriculum Mentorship

01/2022-Present Mukund Jayaraju, University of Michigan, Curriculum Mentorship

01/2022-Present Sadie Hertz, University of Michigan, Curriculum Mentorship

High school Student

01/2013-01/2013 Jesse Mansoor, Gilmore Academy, Shaker Heights, OH, Advancing toward degree.

01/2014-01/2015 Sarah Socrates, Gilmore Academy, Shaker Heights, OH Advancing toward degree

01/2015-01/2015 Adrian Powell, New Tech High School, Cleveland, OH, Currently, Advancing toward degree

01/2015-01/2016	Richard Alvarez, Shaker Heights High School, Shaker Heights, OH Currently, advancing toward degree.
01/2015-01/2017	Daniel Shanhuai, Beachwood High School, Currently, medical student SUNY Albany, Albany, NY
01/2016-01/2017	Kortney Mave, Bera Midpark High School, Currently, Undergraduate student The Ohio State University
01/2017-07/2018	Lily Kwiatkowski, John Jay High School, Cleveland, OH, Currently, Joan C. Edwards Scholar and medical student Case Western Reserve University, Cleveland, OH,
01/2017-01/2018	Sejal Sangani, Hathaway Brown, Cleveland, OH, Currently, Undergraduate student, University of Pennsylvania, Philadelphia, PA,
01/2017-07/2018	Kareem King, Charles Brush High School, Currently, Undergraduate student, Harvard University, Boston, MA
03/2022-Present	Dylan Carvette, Green Hills High School, Currently, Undergraduate student, Undergraduate student, University of Michigan, Ann Arbor, MI
06//2023-Present	Justin Baldassere, Hastings-on-the Hudson, New York, Currently, High school student
06/2023-Present	Fiza Ali, Green Hills High School, Currently, High school student

Teaching Activity
Institutional

01/2013-07/2018	Department of Genetics and Genomic Sciences, Lecturer, GENE 500/504 Advanced Eukaryotic Genetics I, Case Western Reserve University
01/2014-07/2018	Graduate School, Small group facilitator, IBMS 500 On Becoming a Professional Scientist, Case Western Reserve University
01/2016-07/2018	Medical School First-Year Curriculum, IQ (inquiry group) team facilitator, Block 2 Medical School, The Human Blueprint (Molecular Biology and Genetics), Case Western Reserve University
01/2016-07/2018	Department of Pathology and Biochemistry, Course Director, BIOC 420/PATH 420 Current Topics in Cancer, Case Western Reserve University
01/2017-07/2018	Medical School, Year 2-4 Curriculum, IQ (inquiry group) team facilitator, Block 6 Medical School, Cognition, Sensation, and Movement
01/2017-07/2018	Department of Pharmacology, Lecturer, PHARM 528 Contemporary Approaches to Drug Discovery, Case Western Reserve University
2019- present	Cancer Biology 554 lecturer, Cancer Biology Graduate Program, University of Michigan, Ann Arbor, MI
2020-present	Pharmacology 502, University of Michigan, Ann Arbor, MI
2020- present	Cancer Biology 800, Co-Director, Cancer Biology Graduate Program, University of Michigan, Ann Arbor, MI
2022-present	PIBS 503, Responsible Conduct of Research, University of Michigan, Ann Arbor, MI

Analisa DiFeo, PhD

Dissertation Committee

01/2013-4/2019	Samuel Li, Genetics and Genomic Sciences, Case Western Reserve University, Committee Member
01/2013-02/2020	Megan Forrest, Genetics and Genomic Sciences, Case Western Reserve University, Committee Member
01/2013-03/2018	Elizabeth Akinbiyi, Pathology, Case Western Reserve University, Committee Member
01/2013-12/2019	Abby Perl, Pharmacology, Case Western Reserve University, Committee Member
01/2013-Present	Christine Lee, Pharmacology, Case Western Reserve University, Committee Member
01/2013-05/2019	Caitlin O'Connor, Pharmacology, Case Western Reserve University, Committee Member
01/2013-04/2021	Tian He, Biochemistry, Case Western Reserve University, Committee Member
01/2014-01/2018	Valery Adorno-Cruz, Pharmacology, Case Western Reserve University, Committee Member
01/2015-10/2019	Alyssa La Belle, Pharmacology, Case Western Reserve University, Committee Member
01/2015-01/2018	Jennifer Brancato, Pharmacology, Case Western Reserve University, Committee Member
01/2017-06/17	Ryan Hansen, Biomedical Engineering, Case Western Reserve University, Committee Member
01/2013-04/2017	Christina Franke, Biomedical Engineering, Case Western Reserve University, Committee Member
01/2012-04/2017	Anna Czapar, Pathology, Case Western Reserve University Committee Member
01/2012-09/2017	Benjamin Bryson, Pathology, Case Western Reserve University, Committee Member
01/2016-07/2018	Melissa Shively, Pharmacology, Case Western Reserve University, Committee Member
2018-2019	Cayman Novak, Biomedical Engineering, University of Michigan, Committee Member
01/2019- 04/2022	Jennifer Jimenez, Cancer Biology University of Michigan, Committee Member
2019-present	Eric Horst, Biomedical Engineering, University of Michigan, Committee Member
2020	Eziwoma Alibo, Cancer Biology, Icahn School of Medicine at Mount Sinai, External Thesis Reviewer
2018-2020	Emily Sherman, Pharmacology, University of Michigan, Committee Member
2021- present	Terrence Haanen, Cancer Biology, University of Michigan, Committee Chair
2021- present	Yating Zheng, Pharmacology University of Michigan, Committee Member
2021-present	Alan Kelleher, Cancer Biology, University of Michigan, Committee Chair
2021-present	Brian Train, Pharmacology, University of Michigan, Committee Member
2021- present	Yun Zhang, Cancer Biology, University of Michigan, Committee Chair
2022- present	Monice Bonilla, Cancer Biology, University of Michigan, Committee Chair
2022-present	Angelo Guilatco, Cancer Biology, University of Michigan, Committee Chair
2022-present	Katie Burkhead, Biomedical Engineering, University of Michigan, Committee Member

Memberships in Professional Societies

Analisa DiFeo, PhD

2006 - Present	Women in Cancer Research (WICR)
2006 - Present	American Association for Cancer Research (AACR)
2023 -Present	American Association for the Advancement of Science (AAAS)

Committee/Service

National

2011 - present	The Young Scientist Foundation, Scientific Advisory Board, Other, Co-Founder and Chair
2014 - present	Colleen's Dream, Scientific Advisory Board, Other, Member
2015	Gynecologic Cancer Symposium, Gathering Place, Other, Co-Chair
2015 - 2018	Northeast Ohio Science and Engineering Fair, Cleveland, OH, Other, Poster Judge
2016	Cancer Stem Cell Conference, Other, Co-Director
2017	Gynecologic Cancer Symposium, Gathering Place, Other, Member
2018	Cancer Stem Cell Conference, Other, Co-Director
2022-present	Michigan Ovarian Cancer Innovation and Science Consortium (MOSAIC), Director
2022-present	MIOCA Board of Trustees, Board Member
2022- present	American Cancer Society ResearchHERs, American Cancer Society, Ambassador

Institutional

2012 - 2018	Fellowship Interviews for Department of OB/Gyn Gynecological Oncology, Case Western Reserve University, Other, Member
2012 - 2018	MD/PhD Admission Interviews for MSTP program (Prospective MD/PhD Students), Case Western Reserve University, Other, Applicant Interviewer
2012 - 2018	MD Admission Interviews for MD program, Case Western Reserve University, Other, Member
2012 - 2018	PhD Admission Interviews for BSTP program (Prospective PhD Students), Case Western Reserve University, Other, Applicant Interviewer
2013 - 2018	CWRU Faculty Senate By-laws Committee, elected to serve for 2 terms, Other, Member
2013 - 2018	Medical Student Training Program Retreat, Case Western Reserve University, Other, Poster Judge and Panelist
2016 - 2018	Cell and Molecular Biology Training Program, Case Western Reserve University, Steering Committee
2016 - 2018	Molecular Therapeutic Training Program, Case Western Reserve University, Steering Committee
2017 - 2018	Council on Biomedical Research, Case Western Reserve University, Vice Chair of Infrastructure Council
2017 - 2018	Committee on Drug Development and Resistance, Case Western Reserve University, Member

2019-present	Program in Biomedical Sciences (PIBS) Interview Committee, The University of Michigan, Ann Arbor, MI
2019	Undergraduate Research Opportunity Program (UROP) Career Fair Speaker, The University of Michigan, Ann Arbor, MI
2019	One Day Closer, Kick-Off Speaker, Rogel Cancer Center, The University of Michigan, Ann Arbor, MI
2019-2022	Senate Assembly, The University of Michigan Medical School, Ann Arbor, MI
2019-present	Poster Judge, Cancer Biology Spring Symposium, Rogel Cancer Center, The University of Michigan, Ann Arbor, MI
2019-present	Grant reviewer, post-doctoral fellowship competition, Rogel Cancer Center, The University of Michigan, Ann Arbor, MI
2019-present	Cancer Biology Graduate Program Admission's Committee, The University of Michigan, Ann Arbor, MI
2019-present	Physician Scientist Training Program Interview Committee, Michigan Medicine, Ann Arbor, MI
2019-present	Cancer Biology Graduate Program Steering Committee, The University of Michigan, Ann Arbor, MI
2019-present	Program in Biomedical Sciences (PIBS) Inclusive Committee, The University of Michigan, Ann Arbor, MI
2019-present	Diversity Ambassador, Program in Biomedical Sciences (PIBS) program, The University of Michigan, Ann Arbor, MI
2020-present	Pathology Physician Scientist Training Program Interview Committee, Michigan Medicine, Ann Arbor, MI
2020-present	Biomedical Research Council (BMRC) Member, The University of Michigan, Ann Arbor, MI
2020-present	Rackham Mentoring Awards Committee member, The University of Michigan, Ann Arbor, MI
2020-present	Poster Judge, Pathology Symposium, The University of Michigan, Ann Arbor, MI
2021-present	Rogel Cancer Center Cancer Research Committee (CRC) member, The University of Michigan, Ann Arbor, MI
2021-present	Medical Affairs Advisory Committee (MAAC) member, The University of Michigan, Ann Arbor, MI

2021- present	Wellness committee, Department of Pathology, The University of Michigan, Ann Arbor, MI
2021	Faculty participant and mentor, Developing Future Biologists Virtual Fall Research Symposium Program, The University of Michigan, Ann Arbor, MI
2022	One Day Closer, Career Panel, Rogel Cancer Center, The University of Michigan, Ann Arbor, MI
2022-Present	Member, Animal Care and Use Faculty Advisory Committee, University of Michigan, Ann Arbor, Michigan
2022	Pathways Fellowship speaker, Rogel Cancer Center, The University of Michigan, Ann Arbor, MI
2022-present	Advisory committee of the T32 Training Grant (NHLBI) for Hematology, The University of Michigan, Ann Arbor, MI
2021-present	Medical Affairs Advisory Committee (MAAC) Chair, The University of Michigan, Ann Arbor, MI
2023- present	Rogel Training, Education, and Career Development (TrEC) internal advisory council, The University of Michigan, Ann Arbor, MI
2023	MIOCA 5K to Teal Run Kick-Off Speaker, The University of Michigan, Ann Arbor, MI

Scholarly Activities

Presentations

Other

1. *KLF6 and KLF6-SV1 Regulate Ovarian Cancer Progression and Dissemination Identification of a Novel KLF6/E-cadherin Pathway.* April 2004, AACR Annual Meeting, Washington D.C.
2. *Essential role of KLF6-SV1 in regulating tumor cell apoptosis and greatly increasing median and overall ovarian cancer survival: identification and pre-clinical targeting of a novel prosurvival/anti-apoptotic protein.* Plenary Presentation: Experimental and Molecular Therapeutics. April 2008, AACR Annual Meeting, San Diego, CA
3. *Uncovering Novel miRNA's Driving Ovarian Cancer Chemoresistance* University of Michigan Cancer Center Grand Rounds, February 2011, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI
4. *Uncovering the Paths of Ovarian Cancer Chemoresistance.* Department of Genetics Seminar Series, March 2011, Icahn School of Medicine at Mount Sinai, New York, NY
5. *KLF6-SV1 is a Novel Uterine Leiomyosarcoma Gene: From Transgenic Mouse Model to Human Disease.* Focused Plenary Presentation, Society of Gynecologic Oncologist Annual Meeting, March 2011, Orlando, Florida

6. *Dissecting the Mechanisms of Ovarian Cancer Development and Chemotherapy Resistance.* Cancer Center Seminar Series, April 2011, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH
7. *miR-181a driven repression of Smad7 induces epithelial-to-mesenchymal transition and is associated with poor outcome in late-stage epithelial ovarian cancer.* AACR Noncoding RNAs and Cancer Conference, January 2012, Miami Beach, FL.
8. *microRNA-181a activates TGF-beta and is associated with poor outcome in epithelial ovarian cancer.* Ovarian Cancer: Molecular Mechanisms and Personalized Medicine Symposium, May 2012 UPMC Cancer Pavilion, Pittsburgh, PA
9. AACR: Advances in Ovarian Cancer Research: From Concept to Clinic conference, September 2013 Miami, Florida
10. *Development of Small Molecule Activators of Protein Phosphatase 2A (SMAPs) for the Treatment of High-Grade Serous Ovarian and Uterine Cancer,* June 2015, EACR-AACR-SIC conference Florence, Italy
11. *Identification of functional microRNA: mRNA pathways driving ovarian cancer chemotherapy resistance and disease recurrence.* Cancer Biology Seminar Mario Negri Institute, June 2015, Milan, Italy
12. *B-catenin as a TIC therapeutic target in epithelial ovarian cancer.* AACR Special Conference on Advances in Ovarian Cancer Research: Exploiting Vulnerabilities October 2015, Orlando, FL
13. *Ovarian Cancer pathogenesis: What we know and where we need to go.* NTA Technical Symposium, Ohio Aerospace Institute (OAI), June 2016, Cleveland, OH
14. *Ovarian Cancer pathogenesis: What we know and where we need to go.* NTA Technical Symposium, Ohio Aerospace Institute (OAI), June 2016, Cleveland, OH
15. *Passion is Contagious: Uniting researchers and physicians in pursuit of a common mission.* Main Stage Presentation, Healthcare Businesswomen Association Annual Meeting, November 2016, St. Louis, MO
16. *miR-181a: At the crossroads of signal transduction driving ovarian cancer initiation, metastasis, and drug resistance.* The Cleveland Clinic Lerner Research Institute, Cancer Biology Seminar Series, December 2016, Cleveland Clinic Foundation, Cleveland, OH
17. *Update on Biomarkers of Ovarian Cancer,* Gynecological Cancers Forum, 04/2017, Cleveland Clinic
18. *microRNAs: Small but powerful Drivers of Ovarian Cancer pathogenesis.* Grand Rounds Department of Medicine, June 2017, Washington University, St. Louis, MO
19. *Novel approaches to targeting microRNAs.* RNA Therapeutics Symposium, August 2017, Center for RNA Sciences and Therapeutics, Case Western Reserve University

20. *microRNAs: Small but powerful Drivers of Ovarian Cancer pathogenesis*. Department of Pathology Seminar Series, November 2017, University of Michigan, Ann Arbor, MI
21. *miR-181a: At the crossroads of signal transduction driving ovarian cancer initiation, metastasis, and drug resistance*. Sidney Kimmel Cancer Center Seminar Series, December 2017, Thomas Jefferson University, Philadelphia, PA
22. *microRNAs: Small but powerful Drivers of Ovarian Cancer pathogenesis*. February 2018, Cancer Center Seminar Series, Medical College of Wisconsin
23. *microRNAs: Small but powerful Drivers of Ovarian Cancer pathogenesis*. July 2018, Society for the Study of Reproduction (SSR) 51st Annual Conference, Invited Speaker
24. *A miRNA-mediated approach to dissect the complexity of tumor-initiating cell function and identify miRNA-targeting drugs*. Cancer Stem Cell Conference, Cleveland, OH, Invited Speaker, August 2018
25. *A miRNA-mediated approach to dissect the complexity of ovarian tumor-initiating cells and identify miRNA-targeting drugs*. Pathology for Investigators, Students and Academicians (PISA) 2018 Annual Meeting, Ann Arbor, MI, Invited Speaker, October 2018
26. *A miRNA-mediated approach to dissect the complexity of ovarian tumor-initiating cells and identify miRNA-targeting drugs*. Gordon Research Conference (GRC) on Hormone-Dependent Cancers: Small and Big Data, Invited Speaker, August 2019
27. *miR-181a initiates and perpetuates oncogenic transformation through the regulation of innate immune signaling*. AACR-Advances in Ovarian Cancer, Presentation, September 2019
28. *"Small but mighty: Function of microRNA-181a in driving ovarian cancer pathogenesis"* 18th Annual Pathology Research Symposium, University of Michigan, Ann Arbor, MI
29. *microRNAs: Small but powerful Drivers of Ovarian Cancer Pathogenesis*. June 2020, Cancer Therapeutics Seminar Series, UC San Diego, Invited Speaker
30. *Teamwork makes the dreamwork: Uncovering key drivers of ovarian cancer progression and developing novel therapies through effective clinical-translational collaboration*. 30th John R.G. Gosling Lecture, Department of Obstetrics and Gynecology, March 2021 University of Michigan, Ann Arbor, MI
31. *A miRNA-mediated approach to dissect the complexity of tumor-initiation and identify anti-cancer drugs*. Third Annual Precision Health Symposium, September 30, 2021, Michigan State University, East Lansing, MI
32. *Therapeutic Targeting of miR-181a to Modulate Tumor Immune Response*. Keystone Symposium: Small Regulatory RNAs: From Bench to Bedside, May 1-4th 2022, Santa Fe, NM, Invited Speaker

33. *Faculty Spotlight, Inaugural Pathways to Careers in Cancer Care & Research Undergraduate Fellowship Program*, Rogel Cancer Center, July 2022 University of Michigan, Ann Arbor, MI
34. *Modulating tumor immune response, stemness, and treatment resistance by targeting miR-181a*. November 15, 2022, Distinguished Lecture Series in Experimental Therapeutics, MD Anderson Cancer Center
35. *Modulating tumor immune response, stemness, and treatment resistance by targeting miR-181a*. November 10, 2022, Ovarian Cancer Midwest Focus Conference, Minneapolis, MN
36. *Two Birds One Stone: Therapeutic Targeting miR-181a Modulates Cancer Stem Cell-Immune Cell cross talk in Ovarian Cancer*. January 25, 2023, Grand Rounds Center for Research on Reproduction and Women's Health, University of Pennsylvania, PA
37. *Two Birds One Stone: Therapeutic Targeting miR-181a Modulates Cancer Stem Cell-Immune Cell cross talk in Ovarian Cancer*. April 18, 2023, Grand Rounds Center for Research on Reproduction and Women's Health, Sanford University, Sioux Falls, SD
38. *From Patients to Progress: Unraveling Innovative Therapies through Tumor Analysis and Genetic Insights*. October 10, 2023, Ovarian Cancer Research Symposium, Mott Center, Karmanos Cancer Center, Detroit, MI
39. *From Patients to Progress: Unraveling Innovative Therapies through Tumor Analysis and Genetic Insights*. March 7, 2024, Women in Cancer Symposium, University of Michigan, Ann Arbor, MI

Publications/Scholarship

(Co-First Author *; Corresponding author **; Co-Last author ***)

Peer-Reviewed

Journal Article

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EXHIBIT B

MATERIALS REVIEWED AND CONSIDERED

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REPORTS AND DEPOSITIONS

Expert report of Jeff Boyd, PhD, February 25, 2019 (MDL No. 2738)

Supplemental Expert report of Jeff Boyd, PhD, December 27, 2021 (MDL No. 2738)

Supplemental Expert report of Jeff Boyd, PhD, April 4, 2024 (Carl & Balderrama)

Expert report of Matthew Sanchez, PhD, March 26, 2024 (Balderrama)

Expert report of Matthew Sanchez, PhD, March 26, 2024 (Carl)

Rebuttal (Kessler) Expert report of Matthew Sanchez, PhD, April 1, 2024 (Carl & Balderrama)

Rebuttal (Sage) Expert report of Matthew Sanchez, PhD, April 1, 2024 (Carl & Balderrama)

Expert report of Gregory Diette, MD, MHS, April 4, 2024 (Carl & Balderrama)

Expert report of Juan Carlos Felix, MD, April 2, 2024 (Balderrama)

Expert report of Juan Carlos Felix, MD, April 2, 2024 (Carl)

Expert report of Michael A. Finan, MD, April 3, 2024 (Carl)

Expert report of Christian Merlo, MD, MPH, April 5, 2024 (Carl & Balderrama)

Expert report of Nimesh Nagarsheth, MD, April 3, 2024 (Balderrama)

Expert report of Kathryn E. Osann, PhD, MPH April 5, 2024 (MCL)

Expert report of Paul A. Nony, PhD, CIH, CSP, April 8, 2024 (Carl & Balderrama)

Expert report of Ann G. Wylie, PhD, April 11, 2024 (MCL)

Expert report of Naresh Punjabi, MD, PhD, April 12, 2024 (Carl & Balderrama)

Expert report of Kathleen M. Sutcliffe, April 12, 2024 (Carl & Balderrama)

Expert report of Michael Birrer, MD, PhD, February 25, 2019 (MDL No. 2738)

Expert report of Robert Kurman, MD, February 25, 2019 (MDL No. 2738)

Expert report of Ie-Ming Shih, MD, PhD, February 25, 2019 (MDL No. 2738)

Expert report of Brooke Mossman, February 25, 2019 (MDL No. 2738)

Expert report of Benjamin Neel, MD, PhD, February 25, 2019 (MDL No. 2738)

Daubert hearing testimony of Dr. G. Saed, July 22 and 23, 2019 (MDL No. 2738)

Daubert hearing testimony of Benjamin Neel, MD, PhD dated July 23, 2019 (MDL No. 2738)

Case Specific Expert Report of John Godleski, MD, June 18, 2021 (Judkins)

Case Specific Expert Report of John Godleski, MD, June 21, 2021 (Rausa)

Case Specific Expert Report of John Godleski, MD, June 24, 2021 (Newsome)

Expert Report of Anne McTiernan, MD, PhD, June 24, 2021

Expert Report of Laura Plunkett, PhD, DABT, June 30, 2021

Expert Report of Jack Siemiatycki, MSc, PhD, June 30, 2021

Expert Report of Daniel Clarke-Pearson, MD, July 2, 2021

Case Specific Expert Report of Daniel Clarke-Pearson, MD, July 2, 2021 (Converse)

Case Specific Expert Report of Daniel Clarke-Pearson, MD, July 2, 2021 (Newsome)

Case Specific Expert Report of Daniel Clarke-Pearson, July 2, 2021 (Rausa)

Expert Report of Judith Wolf, MD, July 2, 2021

Case Specific Expert Report of Judith Wolf, July 2, 2021 (Gallardo)

Case Specific Expert Report of Judith Wolf, July 2, 2021 (Judkins)

Deposition Transcript of Judith Wolf, MD, September 13 and 14, 2021 (MDL No. 2738)

Deposition of Daniel Clarke-Pearson, MD, August 26 and 27, 2021 (MDL No. 2738)

Second Amended Expert Report of Anne McTiernan, MD, PhD, November 15, 2023 (MDL No. 2738)

Second Amended Expert Report of Jack Siemiatycki, MSc, PhD, November 15, 2023 (MDL No. 2738)

Second Amended Expert Report of Daniel Clarke-Pearson, MD, November 15, 2023 (MDL No. 2738)

Second Amended Expert Report of Judith Wolf, MD, November 15, 2023 (MDL No. 2738)

Second Amended Expert Report of Rebecca Smith-Bindman, MD, November 15, 2023 (MDL No. 2738)

Amended Expert Report of David A. Kessler, MD, November 15, 2023 (MDL No. 2738)

Amended Expert Report of Shawn Levy, PhD, November 15, 2023 (MDL No. 2738)

Amended Expert Report of William Sage, MD, JD, November 15, 2023 (MDL No. 2738)

Expert Report of Bernard L. Harlow, PhD, and Kenneth J. Rothman, Dr.PH, November 15, 2023 (MDL No. 2738)

Expert Report of George E. Newman, PhD, November 15, 2023 (MDL No. 2738)

Expert Report of Michele L. Cote, PhD, MPH, November 15, 2023 (MDL No. 2738)

Second Amended Expert Report of Laura Plunkett, PhD, DABT, November 15, 2023 (MDL No. 2738)

Supplemental Expert report of Patricia G. Moorman, MSPH, PhD, November 15, 2023 (MDL No. 2738)

Supplemental Expert Report of Sonal Singh, MD, MPH, November 15, 2023 (MDL No. 2738)

DOCUMENTS

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Exhibit 2 to Deposition of Ghassan Saed, PhD, January 23, 2019 (MDL No. 2738)

Exhibit 3 to Deposition of Ghassan Saed, PhD, January 23, 2019 (MDL No. 2738)

Exhibit 35 to Deposition of Ghassan Saed, PhD, February 14, 2019 (MDL No. 2738)

Exhibit 40 to Deposition of Ghassan Saed, PhD, February 14, 2019 (MDL No. 2738)

Exhibit A39 to Daubert hearing

Plaintiff's Steering Committee's Response and Objections to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents to John J. Godleski, January 22, 2024 (MDL No. 2738)

John J. Godleski Response No. 2 to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents, TalcMDL-Godleski-000024-000074 (MDL No. 2738)

John J. Godleski Response No. 3 to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents, TalcMDL-Godleski-000117-000119 (MDL No. 2738)

John J. Godleski Response No. 7 to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents, TalcMDL-Godleski-000075-000098 (MDL No. 2738)

John J. Godleski Response No. 11-1 to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents, TalcMDL-Godleski-000001-000023 (MDL No. 2738)

John J. Godleski Response No. 11-2 to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents, TalcMDL-Godleski-000099-000116 and TalcMDL-Godleski-000120-000286 (MDL No. 2738)

John J. Godleski Response No. 11-4 to Defendant Johnson & Johnson's Second Set of Requests for the Production of Documents, TalcMDL-Godleski-000287-000340 (MDL No. 2738)

MEDICAL RECORDS

Medical records for Diana Balderrama

Medical records for Linda Bondurant

Medical records for Hillary Converse

Medical records for Anna Gallardo

Medical records for Carter Judkins

Medical records for Tamara Newsome

Medical records for Pasqualina Rausa